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THE EFFECT OF DIET COUNSELLING AND SUPPLEMENTATION WITH A DEFINED FORMULA DIET ON CROHN'S DISEASE

by

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ABSTRACT

Dietary therapy in Crohn's disease (CD) has traditionally been directed at the maintenance of an adequate nutritional status. The role of counselling as primary therapy in CD is not clear. The purpose of the present study was to determine the effects of nutritional counselling on the clinical course of patients with mild to moderately severe CD. One hundred and thirty-seven patients with a mean Crohn's Disease Activity Index (CDAI) of 112±97 were randomized into either a group receiving monthly dietary counselling (C), or a group not receiving counselling (NC). Regular and usual medical management was maintained throughout the study. The aim of counselling was to normalize the patient's nutritional status as indicated by their intake and by anthropometric and laboratory measurements. All patients were assessed at entry and at three-month intervals for one year.

C was associated with improvements in the intake of energy, protein, calcium, phosphorous and vitamins A, B_1, B_2, B_3, B_{12} and ascorbic acid. The CDAI of C decreased significantly ($p < 0.05$) in the first three months and this improvement was maintained throughout the study, whereas the CDAI of NC remained unchanged. C was also associated with significant decreases in two more objective indices of disease activity, the Harvey and Bradshaw modified CDAI and the Oxford index. Of the patients who entered the study with active disease (CDAI >150), 22% of C went into remission by six months versus 8% of NC ($p < 0.05$). Conversely, 12% of C versus 18% of NC suffered a relapse during this time, i.e. their CDAI rose above 150. There was a decrease in the time lost from work in C versus NC, 297 versus 526 days by six months ($p < 0.01$), and in the number of days in hospital, 155 versus 216 by six months ($p < 0.05$). No difference was noted in the amount of surgery required, but C was associated with decreases in the proportion of patients taking Prednisone and Salazopyrin® and in the number of patients who were able to decrease the dose or stop taking each medication.

At six months, patients were further randomized into groups taking or not taking the supplement Ensure® (E). This resulted in four study groups: C+E, C, NC+E and NC. Males were prescribed three cans per day (750 kcal) and females were prescribed two cans per day (500 kcal), in addition to their normal food intake. Compliance to E was poor due to a high incidence of side-effects ascribed by the patients to the consumption of E. Compliance of E ingestion was improved by counselling. However, compliance to E was not associated with an improvement in nutrient intake due to a decreased food intake. Anthropometric and laboratory assessments were not affected by the consumption of E. Smaller amounts of E were associated with decreased CDAI ($p < 0.10$) but larger amounts of E showed no benefit. Need for medication was not affected by compliance to E. E was associated with a decreased need for surgery and a reduced length of hospitalization.

In summary, individualized diet counselling was associated with an improved clinical course of patients with CD, and thus plays a role in the medical management of this disease. Low intakes of Ensure® obscured the significance of the clinical benefits observed by this form of therapy.

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INTRODUCTION

Crohn's disease (CD) is a chronic, progressive, inflammatory disorder which can involve any portion of the gastrointestinal tract. Extraintestinal complications are common (264). Since the time when CD was first described in 1932 by Crohn, Ginzberg and Oppenheimer, the prevalence of CD in North America and Europe has increased rapidly to the current value of approximately thirty patients per 100,000 population (43). The etiology of CD is unknown. Investigations have centered on potential genetic, psychogenic and immunological factors, as well as on the possible role of transmissible agents and early childhood experiences (230). The disease is characterized by skip lesions in the small and large bowel, a tendency to fistulae formation, and a high incidence of recurrence after surgery. There is no known cure for CD. Medical therapy is directed at improving the patient's symptoms and attempting to reduce the disease activity and its complications.

Nutritional disturbances also complicate CD. The mechanisms for nutrient deficiency include inadequate intake, malabsorption, excessive losses, increased requirements and interference by therapeutic drugs (131) (240). Reports of nutrient deficiencies in CD range from vitamin A (185) (226) to zinc (91) (196) (255). Laboratory data reveal a wide spectrum of abnormalities, from frequent mild deficiencies such as low serum folate concentrations (83), to infrequent severe deficiencies resulting in scurvy (175) and metabolic bone disease (76) (272).

The role of food in the etiology of CD has been actively debated and is often downplayed (165). However, it is intriguing to speculate that poor nutritional status might alter immune function (59) and thereby influence the activity or progression of the disease. Alternatively, food in the lumen of the intestine may alter the structure and the function of the gastrointestinal tract (92), and may influence the clinical course of the disease.

Accordingly the objectives of this study were:

1. to determine the effects of dietary counselling and supplementation on the Crohn's Disease Activity Index (CDAI) and other indices of CD activity, on the requirement for medications, and on the general state of health and well-being such as the need for surgery, the number of days in hospital and the amount of time lost from work;

2. to survey the nutritional status of patients with CD at several time points over a six month period;

3. to determine the effects of dietary counselling and supplementation with a chemically defined diet on nutritional, anthropometric and laboratory measurements; and,

4. to correlate selected nutritional, laboratory and clinical measurements.

In the literature review, I will first provide an overview of the nutritional status of patients with CD, and will suggest mechanisms by which diet may affect the disease process by influencing gut and immune function. The therapeutic efficacy of enteral and parenteral modes of feeding in CD will be described, and proposed guidelines for planning an adequate oral intake for CD patients will be presented for a number of nutrients. Finally, methods and criteria for evaluating the effectiveness of dietary intervention in CD will be discussed for a number of variables, including nutrient intake, anthropometric, laboratory and clinical levels of assessment.

LITERATURE REVIEW

I. Nutritional Status in Crohn's Disease

There is no evidence to suggest that food directly or indirectly causes CD. Earlier emphasis on a gut allergic reaction to cow's milk proteins has not been substantiated (165). The suggestion by James (140) that Crohn's patients eat more cornflakes for breakfast than do healthy persons, and that this increased consumption may have etiologic significance, has not been supported by further study (11) (193) (218). The etiological importance of an increased intake of refined sugar and sweets (191) has not been demonstrated, although a number of authors have substantiated that patients with CD have a fondness for sugar (152) (193) (194) (200) (216) (265). If a fondness for sugar exists in patients with CD, it may be due to changes in taste acuity associated with zinc deficiency (196). Low fiber intakes, which have been implicated in a number of intestinal disorders (46), similarly have not been shown to cause CD. However, some authors advocate the benefits of a high-fiber diet in patients with this disease (123). Nutritional depletion, however, is a common occurrence in CD and may result from several mechanisms (131) (240):

1. inadequate intake due to misdirected dietary conceptions, the anorexia of disease, altered taste or the fear of eating as a result of the patient's increased pain or diarrhea upon eating;
2. malabsorption resulting from inflammation of the bowel, short bowel syndrome, bacterial overgrowth, bile salt wastage or excessively rapid intestinal transit;
3. excessive losses caused by protein losing enteropathy, fistulae, gastrointestinal bleeding, diarrhea or steatorrhea;

4. increased requirements due to fever, for repletion of depleted body stores, or for growth; and

5. interference of utilization of nutrients by therapeutic drugs such as corticosteroids, sulphasalazine or cholestyramine.

Nutritional complications of CD include protein-calorie malnutrition, vitamin and mineral deficiencies, trace metal depletion, and electrolyte abnormalities. The prevalence of specific deficiencies in CD is illustrated in the following table:

Prevalence of nutritional deficiency in Crohn's disease. (224)

	Prevalence (%)
Macronutrient deficiency	
Weight loss	65-75
Hypoalbuminaemia	25-80
Intestinal protein loss	75
Negative nitrogen balance	69
Micronutrient deficiency	
Anemia	60-80
Iron deficiency	39
Vitamin B_{12} deficiency	48
Folate deficiency	54-64
Calcium deficiency	13
Magnesium deficiency	14-33
Potassium deficiency	6-20
Vitamin A deficiency	11
Vitamin C deficiency	*
Vitamin D deficiency	75
Vitamin K deficiency	*
Zinc deficiency	40-50
Copper deficiency	*
Metabolic bone disease	*

* Reported, but prevalence not described

Abnormal protein-calorie status is characterized by the depletion of subcutaneous fat and muscle mass (107). Inadequate calorie intake over a prolonged period of time has been implicated in the growth failure occurring in 15 to 30% of pre-puberty children affected with CD (156). Protein-calorie malnutrition has also been linked to immunodeficiency syndromes (59) which, in turn, have currently generated much interest as an immunological hypothesis for the etiology or perpetuation of CD (165).

Deficiencies in almost every known vitamin, mineral, trace metal and electrolyte have been reported in the literature at some time as a result of CD (79). Vitamin and mineral deficiencies in CD range from suboptimal hematological or biochemical parameters, to overt clinical symptoms of deficiency. Nutritional depletion may be rapid and severe during an active phase of the disease. The quantitative effect of CD on vitamin and mineral requirements has not been explored in detail, but one might assume that requirements are likely to be increased in CD associated with malabsorption, excessive losses, fever or drug/nutrient interactions (160). Mechanisms for deficiency and guidelines for repletion of selected nutrients will be discussed fully in a later section.

Diet therapy in CD has traditionally been reserved for treatment of a variety of nutritional deficits and for control of symptoms rather than for control of the progress of the disease itself.

Intensive nutritional support was first used in inflammatory bowel disease (IBD) over a decade ago. It was hoped that nutritional deficits could be reversed and that the course of IBD would be altered. A review of the value of nutritional support in IBD (167) reported that total parenteral nutrition and chemically defined diets often accomplished nutritional restitution and a short-term clinical remission. Also, this nutritional support has been associated with decreased morbidity and mortality in patients undergoing surgery. Furthermore, children with CD reestablished linear growth with nutritional supplementation. However, it is not known whether these benefits result from bowel rest, from nutritional repletion, or from an as yet unidentified factor in food or food supplements. The use of defined formula diets and total parenteral nutrition in CD are discussed in detail in III 1. and III 2. Heaton et al (123) have successfully utilized an unrefined carbohydrate, fiber-rich diet as adjunctive treatment in CD. These workers reported fewer and shorter hospital admissions in the diet treated group, as well as a decline in the need for surgery. No other work has been reported on the effects of dietary intake and nutritional counselling on the prognosis of patients with CD.

II. Effects of Diet on Crohn's Disease: Theoretical Considerations

1. Diet and Intestinal Function

Manipulation of the diet may induce changes in intestinal function (92). This seems appropriate, since the gut is the first organ to derive nutrition from food in the lumen. The following section will discuss evidence that gut function can be modified to varying degrees by starvation and protein-calorie malnutrition, by parenteral, enteral or oral modes of feeding, and by the quantity of protein, fat and carbohydrate in the diet.

Adaptive responses by the gut occur at three levels of intestinal function (178):

1. at the structural level, diet can affect the rate of mitosis and cell turnover, the number of mucosal cells along the villus, the morphology of the absorptive surface, and ultimately, the overall length, weight and thickness of the intestine;
2. at the digestive level, diet can modify the digestive enzyme reserve of and hormone release from the small intestine and the pancreas;
3. at the transport level, active and passive mechanisms of nutrient kinetics are amenable to dietary changes.

The mucosa of the small intestine is one of the most rapidly proliferating tissues of the body. In man, cell turnover occurs every four to five days (145). Thus, the gut requires a constant supply of adequate nutrients. Just as deficiencies of iron, folate and vitamin B_{12} may interfere with erythropoiesis and lead to anemia, so it might be anticipated that nutritional deficiencies would interfere with epithelial cell production in the intestine. If the structure or function is disturbed, malabsorption may be the result. A self-perpetuating cycle of intestinal dysfunction, diarrhea, malabsorption and malnutrition may ensue.

The intestinal epithelium receives nutrients directly from the lumen as well as from the bloodstream. The greatest demand for nutrients occurs during cell division in the crypts (15). Animal and human studies have confirmed that increased food intake results in hypertrophy of the villus and hyperplasia of the mucosa, while fasting and starvation may produce mucosal atrophy (145)(282).

Interpretation of the available studies on human malnutrition is difficult. In children, marasmus (combined energy and protein deficiency) and kwashiorkor (severe protein deficiency) have been associated with diarrhea, steatorrhea, disaccharide intolerance and poor vitamin B_{12} absorption (15). However, complicating factors other than the dietary deficiency cannot be ruled out, since much of this research is from areas where tropical sprue, parasites and other gut diseases are common.

Animal studies have shown that the effects of fasting on the small bowel are complex (151). Starvation rapidly reduces mucosal DNA as well as the rate of mitosis and cell migration. This prolongs cell turnover and depletes the number of villi and crypts in the epithelium (15). Some of these effects may be due to a protein deficiency created during starvation. In protein-depleted animals, crypt mitosis decreases and cell generation time is prolonged. Ultimately, the mucosal lining of the stomach and intestine become hypoplastic, the wall is reduced in thickness, and the mucosal biopsies may resemble celiac sprue (94).

The effects of starvation on the gut probably result not only from nutrient deficiencies but from disuse, since it seems certain that the integrity of small bowel mucosa demands the physical presence of food in the lumen (74). This can be shown by surgical isolation of a loop of intestine in which the effects of absent or greatly diminished content of luminal nutrients can be studied without the complication of malnutrition of the animal. In these isolated loops, villus shape changes, epithelial cell production is decreased, and mucosal cell mass and brush border thickness are reduced (15).

Comparisons among parenterally, enterally and orally fed animals also show the importance of an oral intake to the maintenance of the structural and functional integrity of the gut. In animals, intravenous feeding without oral intake is associated with flat villi, and reduces mucosal thickness and gut weight (126)(202). Enteral feeding is also associated with bowel atrophy (202)(290). The decrease in epithelial mass occurs particularly in the distal bowel due to proximal absorption of the elemental nutrients in enteral formulas (202).

Direct stimulation of mucosal growth by luminal nutrients was illustrated by Morin and colleagues (204). In jejunectomised rats, intra-gastric infusion of carbohydrate and protein partially prevented the intestinal mucosal hypoplasia of TPN fed animals. However, fat in the form of long chain triglycerides, supplying 20% of the total daily energy requirement, provided the most potent stimulus for intestinal mucosal growth. Mucosal structure and function was maintained at levels comparable to those seen in rats given a complete solid diet by mouth. Other substances in the luminal contents which may be responsible for maintaining epithelial integrity include pancreatic and biliary secretions into the upper gastrointestinal tract, digestion products of food, bacteria, and the presence of the bulk of the luminal content (15).

Two final mechanisms by which food is thought to maintain gut structure are through the direct stimulation of trophic hormones such as gastrin and cholecystokinin (281)(282)(74) and through a negative feedback mechanism involving an antimitotic messenger called a "chalone" (281)(282). This substance, which inhibits cell proliferation, has been described in a number of body tissues, notably the epidermis. When a fall in chalone concentration is induced by cell loss, such as the exfoliation produced from a meal, mitotic activity is restored.

Thus the physical presence of food in the lumen, and the nutrients in that food, are essential for the maintenance of a normal mucosal structure in the bowel. However, the exact mechanism whereby luminal contents exert their trophic effect is still under investigation (74).

The second level of intestinal function that is affected by diet is the reserve of digestive enzymes. Manipulation of dietary protein, fat and carbohydrate levels have been shown to cause adaptive responses in the supply and activity of many intestinal enzymes. For example, high-protein and high-carbohydrate diets fed to rats produced elevated levels of peptide hydrolases and disaccharidases (195), respectively. A high fat diet given to rats was associated with raised mucosal monoglyceride acyl-transferase levels (16), and lowered jejunal sucrase, maltase and lactase levels (261).

Pancreatic and bile secretions have digestive as well as trophic functions. Both secretions are affected by the presence of fat and protein in the lumen. These luminal constituents influence the synthesis of the secretions and their release into the gastrointestinal tract (180)(71)(199). Pancreatic amylase, protease and lipase levels in animals and man are sensitive to the intake of the corresponding macronutrients (246)(151).

The third level of gut function affected by diet is the alterations in the rate of absorption. Adaptations involving a specific transport mechanism occur much more rapidly than anatomic adaptation in the intestine (151). Mechanisms of adaptation to diet at the nutrient transport level include changes in carrier number or affinity, alterations in passive permeability or in the electrochemical gradient for sodium, changes in the villus site of maximal nutrient uptake (245), alterations in membrane lipids which might affect the carriers, and changes in the dimensions of the unstirred water layer (UWL) (151). For example, the resistance of the UWL is influenced by changes in the total content of dietary lipid (263). In rabbits, UWL resistance was lowered by a high-cholesterol diet; a high-fat diet and a combined high-fat/high-cholesterol diet also lowered resistance compared to a control diet. The jejunal permeability to fatty acids and glucose was found to be highest in the high-cholesterol diet, while cholesterol absorption was decreased in animals fed the high-cholesterol diet. Passive diffusion through the UWL is the rate-limiting step in the absorption of fatty acids. However, the clinical effect of these findings on nutrients whose rate-determining step is hydrolysis, such as lactose, is unclear.

Thus, diet influences the digestion and absorption of nutrients as well as the morphology of the intestinal epithelium. To conclude this section by way of illustration, the contrasting patterns of intestinal adaptation have been compared for calcium, iron, sugar and amino acids (151). Dietary calcium and iron depress calcium and iron uptake, respectively. Conversely, dietary carbohydrate stimulates sugar uptake. For example, feeding fructose enhances the uptake of fructose but not glucose. Changes in dietary protein intake stimulates intestinal amino acid uptake only when the animal's intake is above the minimum level required for maintenance and health. How can these differing effects of diet be unified into a physiologically appropriate pattern? Calcium and iron are nutritionally essential but absorbed quantities beyond the daily nutritional requirements are of no use. As long as body stores of these minerals are adequate, an increase in dietary intake and gut concentration permits daily requirements to be met with fewer carrier molecules. Thus the carrier is repressed with increasing dietary availability of its substrate. In contrast, dietary glucose is not essential, but is merely a readily available source of calories. Maintenance of the molecular machinery to absorb and process carbohydrate represents an ongoing biosynthetic expense that is justified only by a payoff in calories. Thus, mechanisms have evolved to suppress the digestive enzyme and transport systems when the payoff drops. In short, calcium, iron and sugar absorption all are suppressed when they become useless, but they become useless under opposite circumstances of deficiency and excess.

Amino acids follow either of these two above patterns, depending on the dietary protein level. Once dietary protein intake is adequate to supply the body's needs for nitrogen and essential amino acids, any further protein intake just serves as a source of calories, like carbohydrates. High protein levels induce more amino acid carriers to take advantage of extra calories. However, it would be disadvantageous to the organism to turn off the amino acid carriers, like sugar carriers, when dietary substrate levels of protein are low. Currently, it is not known whether amino acid absorption goes through a minimum at maintenance protein levels and increases with both more and less dietary protein, or whether amino acid absorption is roughly constant with increasing dietary protein until the maintenance level is reached.

Thus does an intricate mechanism for survival intervene on behalf of the body to cope with fluctuating dietary intake. A margin of safety is provided via compensatory mechanisms among the numerous digestive enzyme and transport systems. Only when dietary deficiencies are severe or prolonged enough to impair the structural integrity of the intestinal mucosa will nutritional status be at risk (246).

Possible roles for improving nutritional status in CD would be to attain and maintain ideal physiologic conditions for efficient gut function, and also to promote intestinal healing, resistance to infection, and intestinal adaptation after surgical resection. The effects of specific nutrients on these processes will be mentioned in later sections: for example, the association of zinc with wound healing (249), folate deficiency with gut structural lesions (10) (112), long-chain triglycerides with intestinal adaptation (204), and a variety of nutrients with immune function (59). It is obvious that there are abundant mechanisms by which normalizing nutrient status might affect the course and prognosis of intestinal disease.

2. Diet and Immune Function

Disturbances in immune mechanisms have been suggested as having a potential etiological role in the pathogenesis of CD (104)(279). In this regard, the relationship between nutritional status and immune response (59) suggests a possible role for diet therapy in the improvement in immune function and the possible alteration in the progress of the bowel inflammation. Nutrient repletion has been effective in restoring immunocompetence in patients with protein-calorie malnutrition (168). It remains to be seen if the immune function or the clinical course of CD might be altered using this approach.

Many facets of host resistance are affected by poor nutritional status. The complement system, opsonic function of plasma, and the intracellular killing capacity of polymorphonuclear leukocytes are adversely affected in severe malnutrition (59). However, cell-mediated immune response is most consistently and severely reduced by malnutrition in which all of the lymphoid organs are atrophied and depleted of lymphocytes (59). The impact of moderate or marginal malnutrition on immunity is less well defined. In this situation, the impairment in immunocompetence would likely be less marked, necessitating sensitive techniques for detection. Also, the proportion of individuals with mild nutrient deficiencies who show immunologic deficits might be relatively small. Nonetheless, there is growing evidence that even mild or moderate nutrient deficits may alter the immunologic response of undernourished children (57).

The effects of individual nutrients on immunocompetence have been extensively reviewed (22)(23)(57)(59). Deficiencies of zinc, iron, magnesium, trace metals, selected amino acids, pyridoxine, folic acid and vitamins E, A and B_{12} may adversely affect immunological status. Deficiencies of most of these nutrients have been noted in CD (224). Furthermore, many of these CD patients will be taking Prednisone to suppress the symptomatic activity of their disease. Glucocorticosteroids affect protein status and immune function, and may possibly augment any potential adverse effects of mild/moderate protein deficiency on gut-associated lymphoid tissue. Overnutrition and obesity also produce subtle deficits in cell-mediated immunity and polymorphonuclear leukocyte function, particularly combined with hyperlipidemia (59). Excesses of polyunsaturated fatty acids have also been shown to produce wide-spread immunologic defects in laboratory animals (22).

Chandra and Scrimshaw (58) suggested that if impaired immunocompetence is a forerunner of susceptibility to infection in malnourished individuals, then it should be possible to use immune response as an index of nutritional status. These workers proposed that immunocompetence is a sensitive and functional barometer of nutritional status, and that subtle improvements or impairments of immune function in response to nutrient status will be reflected sooner than by hematological and biochemical adaptation or by clinical signs and symptoms. A number of authors have incorporated tests of immune status into nutritional assessment profiles (33) (53) (31).

It is likely that tissue-damaging immune reactions in CD are pathogenically important, allowing for the perpetuation of the disease. Immunological mechanisms that have been implicated in the etiology of inflammatory bowel disease include elevated hemagglutinating antibodies, increased incidence of immune complexes, an allergy to some dietary proteins, the presence of lymphocytotoxic antibodies and cytotoxic lymphocytes and, finally, defective cell-mediated immunity (104). Brooks (44) developed an argument for a functional deficiency of IgA as the basis of CD which could account for ulceration, granuloma formation, lymphatic congestion and other features characteristic of CD.

However, to date, there is only limited research which follows changes in immune function with time (182) or with diet therapy in relationship to effects on CD activity. Harries et al (116)(117) improved anthropometric and laboratory parameters of nutritional status in malnourished patients with CD by providing enteral supplementation (Ensure-Plus®) These workers also noted an increase in circulating T-lymphocytes and a decrease in inflammatory activity (measured by serum orsomucoid levels) in these patients. They suggested that nutritional repletion might enhance the patient's ability to suppress inflammation by initiating recovery of cell-mediated immunity. Modest increases in dietary vitamin A enhance resistance to infection in animals (22), and might serve a similar function in CD where vitamin A deficiency has been observed (183). Zinc deficiency has been observed in CD (91), and has been implicated in the poor wound healing seen in this disease (249). Since local application of zinc sulphate to the skin restores immune function and promotes wound healing (102), one can speculate on the role for dietary zinc therapy in promoting gut healing during periods of disease remission.

The responsiveness of the immune system to improvements in nutritional status, both at the level of individual nutrients (22) and in protein-calorie repletion (168), suggests that the body's defence mechanisms can be maintained by promoting optimal nutrient status. It is necessary to establish the relationship between improvements in peripheral immunity and changes in gut associated lymphoid tissue. If gut immunity and bowel inflammation can be influenced by nutritional repletion, the clinical course of CD may be altered.

III. Intensive Nutritional Support In Crohn's Disease

1. Enteral Nutrition in the Treatment of Crohn's Disease.

The use of enterally-administered dietary formulas has been proposed for the management of a number of clinical situations relating to CD where standard medical management has been unsuccessful. Several schemes have been used to classify the diverse formulas that are commercially available, and which vary greatly in protein, carbohydrate and fat sources as well as in osmolality, fat content, viscosity, palatability and cost. In general, three types of products constitute complete feeding mixtures: (1) those with intact protein containing milk (and thus lactose); (2) those containing intact protein and/or protein isolates without lactose, and (3) those containing hydrolysed protein (oligopeptides) and/or amino acids, without lactose. The first two types of products have also been called 'defined formula diets' or 'polymeric feeding mixtures', while those of the third group are usually called 'elemental diets' and are 'monomeric-oligomeric' (224). For purposes of this section, enterally-administered formulas (whether polymeric or elemental) will be referred to as defined formula diets (DFD).

These defined formula diets are extremely low in residue, are non-allergenic and are absorbed almost entirely in the upper small bowel (227). Minimal digestion is required. The fat content of these products is generally about 40 percent of calories, and some contain MCT oil. The vitamin, mineral and electrolyte composition varies, but is usually sufficient to meet the current nutrient intake standards when 1500 to 3000 kcal are consumed (224). In choosing a DFD for use in CD special attention should be paid to the osmolality of the product, the nutritional completeness of the formula, the flavor, the lactose content, the fat source and the amount of digestion required.

Studies designed to evaluate the efficacy of DFD in the treatment of CD all reach similar conclusions - that patients can achieve positive nutritional response and in most cases clinical remission (13) (167)(169)(211). Except when indicated, all of the following studies use elemental formulas. Very little work has assessed the effects of polymeric formulas.

Hyperalimentation by way of DFD has been used successfully for a number of clinical situations in CD: as primary therapy providing bowel rest, in the management of enteric fistulae and partial bowel obstruction, for preparation for surgery or procedures, in cases of severe steatorrhea and in children and adolescents with growth retardation (169).

Voitk et al (270) and O'Morain (210) suggest that these monomeric (elemental) diets be considered primary treatment in acute CD. That is, diet may affect the course of disease. This suggestion is based on observations that indications for surgery would occasionally resolve during the period of nutritional improvement. They speculated that the basis of the benefit of DFD in CD related to nutritional repletion while allowing bowel rest. Logan and co-workers (178) drew similar conclusions and stated that the clinical benefits they observed from the use of elemental diets should not be assumed to be solely the consequence of increased availability of nutrients to the catabolic, undernourished patient. Their finding of reduced protein and lymphocyte losses through the gastrointestinal tract after elemental diet therapy lends support to the bowel rest concept, and demonstrates that dietary manipulation can have a direct effect on small bowel involved with CD. Harries and co-workers (116) (117) reported a repression of inflammatory activity in CD (indicated by reduced serum orosomucoid levels) with supplementation with a polymeric formula (Ensure Plus®). They suggested that the nutritional repletion and recovery of cell-mediated immunity might be beneficial to the patient's ability to suppress inflammation and would, thus, place nutritional therapy with the role of primary therapy in CD. However, due to the fluctuating clinical course of CD, more controlled work is required in this area before the impact of any one mode of therapy on the course of the disease can be fully appreciated.

The usefulness of DFD in the management of enteric fistulae seems well established (222)(286)(54)(228). The mechanism is thought to be a reduction of the volume of small bowel content which diminishes fistula output and leads to fistula closure (49)(286). Additionally, electrolyte and nitrogen balance may be attained, improving the patient's surgical risk if spontaneous closure does not appear (286). Unfortunately, in one study the healed fistulae of one study reopened in many patients with the reintroduction of food (54).

With partial bowel obstruction, such as frequently occurs in patients with CD, these low residue diets may permit improved oral nutrition while minimizing the postprandial distress and bowel distension associated with the intake of a regular diet. Bowel rest may permit healing and resolution of the obstruction where obstructive symptoms are due to inflammation and edema (169)(228). DFD have also been used successfully to achieve preoperational nutritional rehabilitation, to minimize post-surgical complications and, in some cases, to delay surgery in CD patients (50)(270)(222). Controlled studies are needed to fully assess the benefits of nutrition repletion in surgical candidates with CD.

Since there is no need for micelle formation in the digestion of the lipids in elemental preparations, diarrhea and steatorrhea due to massive bowel resections, blind-loop syndromes and active inflammation may be amenable to treatment with elemental diets (169)(271)(228). Finally, reversal of growth retardation and delayed sexual maturity has been achieved by intensive oral nutritional therapy, in which the food intake was supplemented with an elemental preparation (162) (164) (203). Restoration of dietary intake relative to metabolic needs is credited with the benefits associated with hyperalimentation in these children.

Palatability is the major problem encountered with the oral administration of elemental diets. Additionally, the high osmolality may produce diarrhea in some patients; nausea, gastric retention, cramps and vomiting have also been noted (169)(85)(227). Fairfull-Smith and co-workers (85) compared elemental and nonelemental (i.e. polymeric) diets provided to patients with small bowel impairment. They observed that the nonelemental, lower osmolality diet was better tolerated in those patients with mild to moderate bowel dysfunction, but in patients with severe bowel abnormalities elemental diets seemed to be better tolerated. However, the high osmolality of these diets still accounted for many adverse reactions and the authors advised that the cheaper, nonelemental diets be the initial formula to be dispensed. It should be noted that some of the newer elemental formulas have osmolalities similar to non-elemental diets. For example, Ross Laboratories produces Vital®, an elemental product, with 460 mOsm/L which resembles their non-elemental product, Ensure®, containing 450 mOsm/L. Jones et al (148) found the incidence of gastrointestinal side-effects to be evenly distributed between elemental and polymeric diet groups. However, they found polymeric diets to be the more appropriate nutritional source in patients with normal gastrointestinal function. They observed that protein repletion occurred more effectively with the polymeric diet than with the isonitrogenous, isocaloric elemental diet. Fairfull-Smith et al (85), on the other hand, reported no difference in nitrogen balance between the two diets in their patients.

One final concern with DFD is based on the assimilation of the product in the jejunum, leaving the distal small bowel without dietary challenge and stimulation. Elemental diets have been associated with abnormal villus morphology, impaired cell renewal, reduced mucosal mass and decreased absorptive capacity of the ileum (202). Buts et al (52) reported that structural and functional adaptation failed to occur in the distal gut of rats with a "short bowel" when they received DFD or total parenteral nutrition, whereas rats given an isocaloric macromolecular diet did demonstrate adaptation. This work suggests that DFD be used in conjunction with an oral food intake wherever possible, and that patients having undergone resection be returned to an oral food intake as soon as is feasible.

2. Parenteral Nutrition in the Treatment of Crohn's Disease.

Some form of enteral nutrition support is usually preferrable for uncomplicated inflammatory bowel disease (IBD) since enteral feeding, as opposed to parenteral modes, allows for some maintenance of gut function and integrity, and is relatively easy, safe and inexpensive. However, total parenteral nutrition (TPN) has transformed the treatment for patients with severe anatomical or functional disorders of the gastrointestinal tract that preclude adequate nutrition. Such disorders relating to CD include severe, acute inflammation, total obstruction, short-bowel syndrome, paralysis of the bowel and high enteric fistula. A review of published reports on the use of TPN in IBD by Kushner and Craig (167) tabulates the various indications for TPN for a number of studies. These indications include, in addition to those listed above, medical failure and pre- or post-operative nutritional support. Studies have indicated that CD patients benefit from TPN to a greater extent than do patients with ulcerative colitis (167).

As with enteral hyperalimentation, the aim of parenteral feeding is to enforce bowel rest while maintaining nutritional status, in the hope that patients will improve symptomatically as a result of decreased mechanical, physical and chemical activities of the bowel. Relief of diarrhea and pain, and improved sense of well-being are the most consistent clinical indications of response to bowel rest. Improvement with TPN when used as primary or adjunctive therapy is generally underway in seven to ten days (84). TPN can also promote a positive nutritional response, as determined by weight gain, a rise in albumin or total body protein and a positive nitrogen balance, in 75 to 100 percent of patients with IBD (167)(84). It should be noted that weight gain used as a sole indicator of nutritional response to TPN is insufficient and can be misleading. Weight gain in excess of one kilogram per week (84) is likely to be due to fluid retention and may not correlate with increases in lean body mass (128).

In a number of series reviewed by Kushner and Craig (167) and by Elson et al (84), 60 to 100 percent of patients with CD experienced short-term remission while receiving TPN; 5 to 67 percent of patients in these series underwent a prolonged response. The discrepancy in findings among these studies may be partly explained by the differing characteristics and disease activities of the patients under study. One-half to two-thirds of Crohn's patients were able to avoid surgery during TPN therapy (84)(173). In those patients in whom surgery was required after a course of parenteral nutrition, the incidence of post-operative complications and surgical mortality was low, ranging from five to seven percent (173). As with enteral diet therapy, parenteral feeding has been useful in reversing growth arrest in children with CD (75)(167). Long-term parenteral nutrition has been used successfully since 1971 (141) and results in improved nutritional indices, restored sense of well-being and reduced hospitalizations in patients with IBD (167).

Virtually all published reports on the use of TPN in IBD, however, are uncontrolled, retrospective studies involving small numbers of patients and containing poor long-term follow up. The unpredictable nature of CD and the absence of control groups has raised questions about the validity of the results of these reports. Ostro, Greenberg and Jeejeebhoy (212) presented results of a retrospective analysis of 100 CD patients treated with TPN and complete bowel rest, and compare their findings with two previous studies acting as a control. A clinical remission was achieved in 77 patients given TPN. They compared this rate with that of placebo-treated and prednisone-treated patients in the National Cooperative Crohn's Disease Study (NCCDS) (256), where the remission rate after one year of observation was 18% and 36% respectively, and secondly with a Swedish study (268) where the administration of metronidazole (Flagyl) was associated with a remission rate of 47% among those patients not lost to follow-up after one year. Ostro and colleagues (212) concluded that a formal randomized trial is warranted to test the hypothesis that TPN and bowel rest may exert greater clinical benefits than placebo alone, or than prednisone or metronidazole. For further comparison, the recently completed European Cooperative Crohn's Disease Study (187) assessed the effectiveness of sulfasalazine, 6-methylprednisolone, or a combination of these two medications. Positive outcomes (either unchanged or improved course of disease) after two years of treatment ranged from 15 to 77% at the various study centers, compared to the placebo range of 10 to 34%. Differences in patient characteristics account for much of the discrepancy in findings among the various study centers.

One controlled trial has been completed which assessed intravenous hyperalimentation and total bowel rest as adjunctive therapy in acute colitis (72). In 27 patients with ulcerative colitis and 9 with CD, the intravenous hyperalimentation group showed no difference from the control in frequency of surgery or duration of medical treatment. It may be, however, that the 22.5 day mean length of follow-up was not sufficiently long to detect benefits from the hyperalimentation. A major criticism of this study is the small number of patients with CD (167).

There are drawbacks to TPN ; these include technical demands, risk of septicemia, thrombophlebitis, metabolic derangements and high cost, not only in dollars but also in terms of hospital personnel and equipment (75). Deficiencies of various electrolytes, trace elements, vitamins and minerals and essential fatty acids have been described after TPN therapy (90)(147)(248). The adequacy of an intravenous supply of several water soluble vitamins was determined for four home TPN patients with CD (137) but complete nutrient needs are not yet fully defined in this disease. Vitamin and mineral requirements for patients on TPN are based on the accepted oral requirements; energy, protein and lipid needs must be calculated individually (147). Driscoll and Rosenberg (75) and Jones (147) discuss practical guidelines for formulating TPN solutions for patients with IBD. A final consideration in the use of TPN is that the absence of an oral intake may worsen gut function since intraluminal nutrition seems to play an important role in maintaining intestinal mucosal integrity (see Section II, 1. Diet and Gut Function).

IV. Proposed Criteria of an Appropriate Diet for Crohn's Disease

The goals of diet therapy in CD are to maintain adequate nutritional status, replenish nutrient stores and aid in the control of symptoms with the possibility of affecting the progress of the disease itself. A CD diet must meet the currently accepted nutritional recommendations for a healthy population. These recommendations include the 1980 American Recommended Dietary Allowances or the 1983 Canadian Recommended Nutrient Intakes. A specific diet for Crohn's patients as a group cannot be planned arbitrarily due to the range of disease severity, the variable nutritional status of patients for a given level of disease activity and the paucity of data on the nutrient requirements of Crohn's patients. A bland, low residue diet has probably been the most widely prescribed diet for patients with inflammatory bowel disease. In patients with small bowel strictures, high fiber foods may cause obstruction, but this probably represents a true risk to relatively few patients. Dietary fiber in CD will be discussed in a later section.

The following sections will describe reports in the literature that may be used to develop adequate dietary guidelines for Crohn's patients. Though the emphasis of diet therapy is on individualization, one can generalize by acknowledging that nutrient requirements will probably be increased in CD when associated with fever, inflammation, fistulae, malabsorption or drug interactions. For control of symptoms, the fat and fiber content of the diet has traditionally been manipulated to ease diarrhea and abdominal pain. To individualize dietary suggestions and to detect problems before overt nutritional disease develops, a full nutritional evaluation of the patient should be conducted which includes a dietary, anthopometric, clinical and laboratory assessment (93) (224).

1. Energy

Depending on disease activity, the presence of steatorrhea and the use of Prednisone (which may be associated with weight gain), energy requirements for Crohn's patients may be increased or possibly decreased in order to maintain ideal anthropometric parameters. Barot et al (17) examined the energy expenditure of twelve hospitalized patients with inflammatory bowel disease (IBD) and found that the resting energy expenditures (REE) of these patients (determined by indirect calorimetric measurements of oxygen consumption and carbon dioxide output) were similar to those reported by Long et al (179) in twenty normal subjects. This suggests either that these IBD patients were not hypermetabolic or that an adaptation to chronic catabolic stress had occurred. Kelts et al (156) also found normal basal metabolic rates in children with CD experiencing growth failure. Barot et al (17) found the calculated basal energy expenditure (BEE), using the Harris-Benedict equations, to be equivalent to the REE in predicting daily caloric requirements. However, these workers found significantly increased energy requirements on a per kilogram body weight basis in patients weighing less than 90% of their ideal body weight, suggesting a relatively hypermetabolic state. Weight loss is, in fact, frequently seen in conjunction with active CD (26). Based on the literature, Barot et al (17) proposed a multiple of BEE to calculate ideal energy intake: 1.75 for minimal to moderately catabolic patients and 2.0 for severely catabolic patients. The adjustment of 1.75 X BEE would provide 45 kcal/kg/day which is consistent with reported values necessary for anabolism. (229)(250).

Extrapolating these findings to the patient with mild or quiescent disease and without steatorrhea, suggests that energy requirements during periods of remission may not differ appreciably from those recommended for the normal, healthy individual. Various studies have suggested that the energy intake by CD patients is either normal (265)(194), high (152) or low (156) compared to controls. Differences in methods to assess dietary intake methods, in patient selection and in control groups probably account for these conflicting results. A generous energy intake might be adviseable during remission to help cushion the effects of anorexia and weight loss that accompany subsequent disease flare-ups, and to replenish nutrient stores.

The assessment of the adequacy of energy intake for an individual with CD is difficult. Body weight, mid-arm circumference, and triceps skin-fold may not reflect energy status if Prednisone therapy has caused fluid retention. The same parameters may not necessarily correlate with lean body mass and nutritional status after hyperalimentation, again because of fluid accumulation. To determine the adequacy of a specific energy intake, certain patient characteristics must be ascertained. The patient's sex, age, present body weight, level of physical activity and degree of CD activity including presence of fistulae or malabsorption, and drug therapy all individualize energy requirements. The underweight patient with only mild CD activity might be treated with the traditional weight gain regime of 500 to 1000 kilocalories above the normal daily intake. This regime should achieve a weekly weight increase of one to two pounds (0.5 to 1.0 kg). However, due to increased metabolic demands of fever and inflammation in active CD, weight gain will be slower for the same increment of caloric excess. Furthermore, as nutritional requirements increase in proportion to the duration and extent of disease flare-up, the dietary intake will tend to decrease in relation to the same factors, making weight loss almost inevitable during active disease. Small, frequent, attractively prepared meals and/or a supplemental chemically defined preparation may help minimize the decline in energy intake.

On the other hand, the CD patient who is overweight due to poor eating habits and low levels of physical activity, combined with relatively inactive disease, or the patient who has experienced fluid accumulation due to Prednisone therapy, presents the problem of whether or not to restrict energy intake. One should seek to ensure that nutrient stores are sufficient to cope with the demands of a potential future flare-up before caloric adjustments are made, since calcium, iron and some other nutrient requirements are difficult to achieve on low caloric diets. Poor food choices and lack of physical activity should be the first issues for counselling the overweight patient with CD. A low salt diet might be helpful to reduce fluid accumulation due to Prednisone, but should be undertaken only if diarrhea is not present. Restriction of calories for the obese CD patient below those calculated by the Harris-Benedict equation should be undertaken cautiously, if at all, unless the patient has been in good health for quite some time.

2. Protein

Development of poor protein status is possible in CD because of contributing factors such as enteric protein loss, malabsorption of amino acids, corticosteroid therapy, tissue catabolism and inadequate intake of dietary protein (98). A number of studies have shown that protein intake in CD patients was not significantly different than controls (152)(194)(265). However, protein deficiency in inflammatory bowel disease is fairly common; depending upon the variable used, the incidence of poor protein status has been assessed at 22% (based on arm muscle circumference), 32% (based on hemoglobin), 35% (based on serum albumin) or 41% (based on serum transferrin or serum pre-albumin) (127).

Jones (147) suggests that protein requirements are elevated by 30% in the depleted patient, by 20 to 150% in the stressed patients (for example, in cases of sepsis, burns or fractures), or by an amount sufficient to replace that lost abnormally from the bowel, kidney or skin. Consequently, a generous protein intake is usually recommended for CD patients to cope with periods of stress; this intake is often set at 1.5 gm per kg ideal body weight per day (98)(240), or roughly 100 gm per day (234).

The protein intake of CD outpatients has been determined in a number of studies: 80 gm (194), 73 gm (265), 89 gm (152), and 86 gm (130). If the commonly accepted measurements reflecting protein status are normal, these intakes are probably sufficient for the group as a whole. These intakes generously exceed the recommended protein intake for the normal healthy individual. The latest Canadian recommendations are set at 61 gm for the adult male and 44 gm for the adult female (220). However, as with energy requirements, the ideal protein intake in CD patients must be calculated individually with consideration given to anthropometric and laboratory data, the frequency of disease flare-ups, the use of glucocorticosteroid therapy and the nutritive value or quality of the protein typically consumed by the individual.

It is important to remember that there is still a need for indicators that are sufficiently sensitive to reveal impending nutritional depletion and, conversely, to detect early response to nutritional support. Thus, the fact that indicators of protein status appear normal at one point in time does not necessarily mean that protein intake is sufficient to meet increased needs. Consequently, when calculating protein needs, one might be safer to err on the generous side rather than on the low side.

One should also keep in mind that energy needs must be met before protein anabolism can occur. In the event of an energy deficit, dietary protein will be used as a source of energy rather than for repleting lean tissue mass (31). Any increase in the protein intake that is recommended to CD patients to cope with increased needs may necessitate an additional allotment of calories in order to maintain nitrogen balance (97). On the basis of extensive studies on man and other species, the magnitude of the change in nitrogen balance is about 0.2 to 0.3 gm of nitrogen for each 100 kcal added to or subtracted from the diet (219).

Changes in protein intake may also affect calcium metabolism. Mahalko et al (184) have found a statistically significant increase in urinary calcium with a moderate increase in dietary protein. The direction of change in calcium balance was toward a less positive balance. This study confirms the variable calciuretic effect of dietary protein observed by many others (184). However, this effect is not found universally. Discrepancies in study outcomes and this variability in the calciuretic effect of dietary protein may result from differences in the phosphate content of the diets, the quantity of dietary protein initially consumed, and the duration of high protein intake (252). The relationship and practical importance of the dietary protein/calcium balance interaction need to be clarified. If calcium intakes were sub-optimal, due to milk intolerance, it is important to establish if the high protein diets prescribed to CD patients would hasten the development of bone problems, already commonly seen in this disease (272).

3. Fat

Fat represents the most concentrated source of energy in the diet. The loss of this energy supply, either through decreased intake or increased fecal loss, may have an adverse effect on energy balance, and ultimately on fat soluble vitamin and essential fatty acid status. On the other hand, low fat diets have been traditionally prescribed for Crohn's patients with steatorrhea or short bowel syndrome. A controversy has developed surrounding the appropriateness of low fat diets for patients with bowel disorders, a debate fuelled by indications that dietary fat may influence intestinal adaptation following resection (204).

Fat intake by outpatients with CD has not been found to differ significantly from that of controls (194)(265)(152). However, with increasing disease activity the fat and total energy intake of the patient might decrease due to decreased food intake. Furthermore, depending on the extent and location of disease, the activity of the disease, and the presence of small bowel resection, the gut may be less able to handle ingested fat, with the result that steatorrhea may occur. Indeed, Dyer and Dawson (79) noted that about one-third of their patients with CD had elevated fecal fat levels. Krawitt et al (166) also showed significant fat malabsorption in 30% of unoperated patients with ileitis; Filipsson et al (89) observed abnormal fecal fat levels in 24% of their patients with less than 30 cm of ileal involvement, in 26% of those with 30 to 60 cm of ileal disease, and in all five of their patients with greater than 60 cm of disease. One hundred centimeters or more of ileum lost to resection or disease has often been taken as an arbitrary cut-off between normal and impaired fat absorption (99). Thus steatorrhea is common in patients with CD.

Suggested mechanisms for this fat malabsorption and diarrhea include a decrease in small bowel absorptive surface area; bacterial overgrowth; bile acid malabsorption resulting in bile salt pool depletion; and, the conversion of malabsorbed long chain triglycerides (LCT) to hydroxy fatty acids by intestinal bacteria. The excessive bile acids and hydroxy fatty acids inhibit intestinal and colonic water and electrolyte absorption and stimulate colonic fluid secretion (6)(69)(2).

Some patients with CD who suffer from steatorrhea have been shown to benefit from a low-fat diet, with a reduction in their fecal fluid and electrolyte losses (6,8)(37)(171). Hessov et al (125) found that the net absorption of calcium, magnesium and zinc was higher when patients were consuming a 40 g as compared with a 100 g fat diet. Ovesen et al (213) also noted an increased secretion of divalent cations in jejunostomy patients consuming a high-fat diet. A possible mechanism for the effectiveness of a low-fat diet is a reduction of the exposure of the colon to unabsorbed bile acids or LCT, both of which may have a cathartic effect (6). A low-fat diet has also been associated with the normalization of hyperoxaluria (7) which often occurs in patients with a short small intestine but with an intact colon. A dietary fat intake of less than 50 gm (5) has been recommended for patients with bowel disease or resection. Medium chain triglycerides (MCT) have been advocated as a replacement for LCT, to provide essential fatty acids and energy requirements (173).

While low-fat, high-carbohydrate diets have been the accepted dietary regime for patients with steatorrhea or short gut syndrome, Simko et al (237,238) have reported favorable effects of a high-fat diet in two patients with massive resection but with at least some functioning jejunum. Diets containing up to 200 gm of fat resulted in increased absorption of dietary fat and bile acids, were well tolerated, did not increase ostomy output, and improved overall nutrition. The basis for the use of a high-fat diet in these patients is that dietary fat is absorbed in the proximal portion of the bowel and that even in large resections of distal small bowel, patients should still be able to absorb considerable amounts of dietary fat. Several studies have shown that 60 to 70% of LCT is absorbed by patients with short bowel syndrome (283)(291)(238). Furthermore, the positive linear relationship that exists between the concentration of lipids in the aqueous phase in the intestinal lumen and the proportion of lipids absorbed by the small intestine was confirmed by Simko et al (238). No mechanism for the increased bile acid absorption in the high-fat diet was presented (238). Simko and co-workers (238) also observed that the high caloric density and low osmolarity of LCT apparently reduced the osmotic load presented to the intestine. This may account for the decrease in stool output compared to a low-fat, high carbohydrate regime. Clearly these observations need to be confirmed.

Woolf and colleagues (287) reported on eight patients with a short bowel, currently in remission from inflammatory bowel disease. The effects of a high-fat (60% of calories) or high-carbohydrate diet (20% of calories from fat, 60% from carbohydrate) were compared in a cross-over design, controlling for fluid intake and timing in relation to meals. The diets were lactose-free and were low in fiber. The results showed that there was no difference in blood chemistry, stool or ostomy volume, zinc, calcium and magnesium balance, urine volume or electrolyte excretion between the two diets. Energy and fat balances were also comparable. These workers concluded that low-fat diets are of no special benefit to CD patients in remission and, hence, dietary restriction was not recommended. As a final argument for high-fat diets, Morin et al (204) outlined evidence suggesting that LCT could be beneficial for the adaptive process of the remaining small bowel of patients with massive resection. The beneficial effect was possibly mediated by trophic humoral or pancreaticobiliary factors. This adaptive process induced by LCT may also trigger the active transport system for bile acids. This could possibly explain the increased bile acid absorption found in the high-fat diet in the work by Simko and co-workers (238). Thus, more controlled studies are needed to ascertain the effectiveness of high-fat diets on larger numbers of patients, and should include work with patients having active disease as well as an assessment of fat-soluble vitamin requirements and losses when on such diets. The possibility of a specific lipid constituent being important in intestinal adaptation also needs to be further examined.

In view of the evidence presented for both a high-fat and a low-fat diet for patients lacking a normally functioning ileum, it is difficult to make arbitrary dietary recommendations. The approach at the University of Alberta Hospital currently is that if the fat intake can be increased without worsening the patient's diarrhea, then higher amounts of fat should be ingested. This will help the patient to maintain their optimal weight and energy intake, to obviate their need for MCT oil, and to enhance the palatability of and therefore their compliance to dietary therapy. Some patients with CD find fatty foods irritating or otherwise unacceptable. In this case the traditional low-fat diet will have to suffice, but may be supplemented with MCT oil. For the symptom-free outpatient with CD, a "normal" proportion of dietary macronutrients should be emphasized, that is, 40% of calories as fat, 46% as carbohydrate and 14% as protein (209).

4. Dietary fiber

Some confusion has developed between the terms "dietary fiber" and "residue". Dietary fiber is defined as "plant polysaccharides and lignin that are resistant to hydrolysis by the digestive enzymes of man". These include plant cell walls, gums, cellulose and pectins. Residue refers to the total contents of the large bowel, and includes not only dietary fiber but also unabsorbed water, bacteria and endogenous secretions into the bowel (28).

Low-fiber diets used to be routinely recommended for a variety of intestinal disorders, including CD. However, there has been little or no evidence for the clinical value of these diets in the treatment of any colonic disease (28). In fact, high-fiber diets are now being used successfully in the treatment of diverticular disease and with variable success in patients with the irritable bowel syndrome. It is speculated that dietary fiber may have at least a protective role in the development of other large bowel disorders, including colonic cancer (174). It has not yet determined which dietary "fiber" might be beneficial in these disorders or if fiber has a role in CD.

A low-residue diet may still be appropriate for those few CD patients with intestinal narrowing or stenosis who are at risk of developing obstruction or toxic megacolon. A low-residue diet is also necessary in the preparation of the clean bowel for surgery or for endoscopic or radiologic examination. However, this diet eliminates fruits and vegetables, juices, nuts, spices, alcohol, and milk. As such, a low-residue diet is nutritionally restrictive and should be supplemented with a vitamin/mineral preparation.

There is little firm evidence that a moderate amount of dietary fiber (DF) mechanically injures the intestinal wall, retards the healing of inflammatory lesions or precipitates obstructions. A fiber-rich, unrefined carbohydrate diet has been used successfully as adjunctive treatment in CD (123) where 32 diet-treated CD patients were followed for a mean of four years and four months. These subjects experienced significantly fewer and shorter hospital admissions and required less surgery than a matched control group. A fiber-rich diet has also been suggested for patients with ulcerative colitis who are particularly apt to develop colonic obstruction with recurrence of disease activity (68), though the high fiber diet was of no value in preventing a relapse. This suggestion must be studied further to assess any risks associated with a high fiber diet in these patients. These findings may not apply to CD.

The effects of fiber in the colon are well documented, and include (66):

1. Increased fecal weight
2. Increased frequency of defecation
3. Shortened transit time
4. Dilution of colonic contents
5. Stimulation of colonic microbial growth
6. Altered nitrogen metabolism
7. Reduced dehydroxylation of bile acids
8. Adsorption of organic and inorganic substances
9. Production of short-chain fatty acids, hydrogen, carbon dioxide and methane
10. Possible effects on hepatic metabolism

Recently, DF has been shown to influence the morphology (258) and function (143) of the small bowel as well. No mechanism was suggested by which the unrefined carbohydrate, fiber-rich diet improved the prognosis of patients with CD in Heaton's study (123). Some possible, though highly speculative actions of fiber in the small bowel which may have implications for inflammatory bowel disease include:

1. dilution by DF of the contents of the intestinal lumen, which may include various drugs, chemicals or food additives that are toxic to the bowel and may precipitate an inflammatory response. In laboratory animals fed low-fiber diets, some of these components were highly toxic but were without deleterious effects when diets high in fiber were fed (161);

2. provision of an alternate source of carbohydrate for the bacterial flora in the gut. This would decrease the utilization of mucin as a carbon source which could impair the integrity of the protective lining of the intestine (231). By this mechanism DF may hinder the invasion of the gut wall by infectious agents;

3. capacity of lignin for binding bile acids, effectively reducing diarrhea in patients with an interrupted enterohepatic pathway due to loss of ileal function (80). The cathartic property of bile acids may be reduced when bound by lignin. However, Kern et al (157) found that bound bile acids were less readily absorbed, and suggested that this interruption in the enterohepatic circulation could become significant in certain patients with massive ileal resection in whom fecal bile salt loss is so large that hepatic compensation is marginal. In this study, though, the fiber-free liquid diet was associated not only with more efficient absorption of bile salts but also greater stool frequency and/or mass, not noted in the 'regular-fiber' or solid diet;

4. regulation of bowel transit time, including a reduction of prolonged transit time as well as a slowing of rapid intestinal transit (215)(121). Hence, DF may relieve diarrhea as well as constipation as do hydrophilic pharmaceutical bulking agents like Metamucil.

Various workers have reported that the DF intake of CD patients is higher than in control subjects (152), less than controls (265) or not significantly different (42)(194). Crude fiber intakes reported by Hodges (130) of 3.8 gm per day were similar to the 4.0 gm found in the Nutrition Canada Survey (209) of adults aged 20 to 39 years living in the prairies. These 'normal' fiber intakes by CD patients mask the probable existence of a subgroup of patients who have voluntarily restricted their fiber intake out of fear of the precipitation of a bowel obstruction, diarrhea or pain, or through access to outdated nutritional advice, or possibly because of actual intolerance to a wide variety of fibrous foods. It has been suggested by Brauer et al (42) that the DF intake may decline as the Crohn's Disease Activity Index increases. If this is the case, laboratory assessment of nutrients found in fibrous foods, vitamins C and A, folate and the B vitamins, would have to be undertaken, and vitamin supplements would need to be given when necessary.

In the high fiber diet study by Heaton et al (123), a mean intake of 33.4 gm per day of DF by the experimental group was not associated with an increase in the incidence of intestinal obstructions. However, very high fiber intakes should be cautioned against until the clinical significance is known of the resulting negative balance of various nutrients, including zinc, copper, calcium, magnesium, iron and silicon (154,155). Such a deficiency would be likely to occur, especially in patients who already have a borderline status in these nutrients. Tasman-Jones et al (258) have observed a trophic role for fiber in the normal maturation of the small bowel in rats. However, Cassidy et al (55) noted deviations from normal jejunal and colonic structure by high-fiber diets, the most severe of which was speculated to have nutritional and pathological consequences. The effects of fiber on bile flow, microbial composition and function, and on the production of regulatory polypeptides were suggested as possible mediators of normal cellular turnover and villous structure in the small bowel (258). On the other hand, Cassidy et al (55) correlated the degree of abnormal histology and possible damage to the colonic mucosa to the bile acid binding capacity of the fiber or resin.

Since both low- and high-fiber intakes may have potentially adverse functional and nutritional effects, it would appear to be reasonable to recommend a moderate fiber intake for the majority of CD patients. In the population at large, an intake of 15 to 20 gm of DF per day has been reported as 'normal' (42)(153)(29)(189). If a low fiber diet has been followed for some time, the patient should be instructed to increase the fiber content of the diet gradually, as tolerated. The DF intake could be considered adequate when the fruit, vegetable and whole grain consumption meets that recommended by Canada's Food Guide. It is possible that no patient may come to any harm as a result of a high-fiber diet, as proposed by Heaton, but such treatment must currently be considered experimental until the promising results of this study are confirmed.

5. Sugar

Interest in the sugar intake of patients with CD has been stimulated by a number of studies reporting that these patients consume more sugar than controls (152)(191)(193)(200)(216)(265). Other workers have not confirmed this difference (42). Mayberry et al (194), in two separate studies, found that the dietary recall method detected a significant difference in the sugar intake of patients with CD, whereas weighing and recording the food as consumed did not. The methodology used in some of these studies has been criticized, i.e.

use of a mailed questionnaire, the retrospective nature of the data, and the use of added sugar as an index of overall sugar consumption. Brauer et al (42) assessed the conflicting results of the various studies and noted that they may be reconciled on the basis of three factors: differences in dietary recall methodology, differences in the control groups, and differences in patient selection. Interest in the intake of sugar by Crohn's patients has been further propogated by evidence that a decrease in sugar intake may be of therapeutic benefit (123)(41).

It is apparent that there is at least a subgroup of patients who consume a high proportion of their total calories as sugar. McClain et al (196) have shown an impaired ability to taste sweetness in patients with CD associated with zinc deficiency. This impaired taste may increase the use of added sugar. The anorexia associated with disease is well-known, but the extent to which the proportions of energy nutrients consumed change in response to disease activity has not been documented. The degree of CD activity was not recorded in most of the studies reporting sugar consumption. Patients suffering from an acute episode of CD may consume a higher proportion of calories as simple carbohydrates (42).

Some authors have suggested that these differences in sugar intake have etiological implications for CD. It has been postulated that habitual, excessive sugar consumption might alter the intestinal flora and the milieu of the intestinal lumen in such a way that the mucosa may be damaged (191). Alternatively, the growth of an infective agent and its invasion of the gut wall may be promoted (265). However, there are no experimental data to support these suggestions. Mayberry et al (194) note that the recent rise in incidence of CD in Great Britain does not correspond with any marked change in sugar consumption in the last fifty years. The most clearly defined drawback to an excesive intake of sugar in CD occurs if the patient is unable to absorb dietary sugar because of a decreased functional surface area or decreased transit time following intestinal resection. Arvanitakis (12) reports diffuse functional and structural small bowel abnormalities of CD that are reflected in reduced levels of sucrase, lactase and other jejunal mucosal enzymes in these patients. Bacteria in the colon split and metabolize the unabsorbed sugars forming organic acids. These acids increase the osmolality and reduce the pH of the colonic contents, contributing to diarrhea. The gases that are also produced can cause flatulence, cramping and abdominal pain (241).

If the preference for sweetness in CD is a true characteristic of this disease, this knowledge can be used in the preparation of, for example, high-calorie and high-protein supplementary drinks using a sugar substitute (such as aspartame) to enhance compliance. The daily sugar intake of Crohn's patients in general should be kept in moderation in order that the overall nutrient density of the foods consumed is maximized, as sweets are often high in calories but low in nutritional value. The amount of sugary foods and drinks should be minimized if jejunal absorption is impaired, as explained previously. If the patient is using a high intake of sweets as a way of regaining lost weight, or to maintain weight during a flare-up, counselling should emphasize that protein and unrefined carbohydrate provide similar calories per gram (approximately four), and are nutritionally superior.

6. Milk Protein and Lactose

There is some evidence of an absence of breast-feeding during infancy and of early weaning in patients who later develop CD (25) or ulcerative colitis (UC)(280). Breast milk contains several factors that may protect against gastrointestinal infections during infancy. Furthermore, it has been suggested that breast milk is essential for the development of a normal immunological competence of the intestinal mucosa. Thus, lack of breast-feeding during infancy might influence the development of inflammatory bowel disease (IBD) later in life (25).

Milk and other dairy products are frequently eliminated from the diet of patients with IBD to help control abdominal symptoms. The constituents in milk which need to be considered include milk protein and the milk sugar, lactose. Wright and Truelove (288) found that 20% of patients with UC were allergic to cow's milk protein, and benefitted from a milk-free diet. However, as an etiologic theory of UC, this finding is controversial due to lack of conclusive immunological evidence (280). In CD, dietary antibodies are seldom observed at high titre in the serum (259). Falchuk and Isselbacher (86) postulated that those studies detecting dietary antibodies were simply observing the secondary phenomenon of increased foreign protein absorption through a damaged mucosal barrier, rather than representing a primary pathogenetic mechanism. An acute inflammatory attack, in damaging the small intestinal mucosa, may act as a triggering mechanism for cow's milk protein intolerance (118). A functional deficiency of IgA in some CD patients (44) may sensitize these patients to foreign proteins, as was suspected in a significant number of children with milk intolerance (118)(119). However, sensitivity to cow's milk protein is not specific to bowel disease, since 0.3 to 7 percent of healthy children also display this trait (241). Thus, there is little convincing evidence for milk protein playing an etiological role in the causation or perpetuation of CD. In the rare instance that a true milk allergy has been diagnosed by the finding of a high titre of circulating antibody to cow's milk protein, a cow's milk-free diet must be implemented. Goat's milk has sometimes been substituted. However, a coincidental lactase deficiency would have to be ruled out since goat's milk contains about the same amount of lactose as cow's milk (277). Harrison et al (119) in fact, have noted a lactose sensitivity secondary to an intolerance to cow's milk protein in 23 out of 25 otherwise healthy children studied. An abnormal immunological reaction within the small bowel mucosa in response to ingestion of cow's milk protein was thought to cause damage to mucosal cells and depression of disaccharidase activities.

Some of the adverse symptomatic effects of milk in IBD may be explained on the basis of a lactose intolerance (163). The reported prevalence of lactose intolerance in CD ranges from 0 to 60 per cent (177), and was 34 per cent in 50 children with this disease (163). The frequency of lactase deficiency in CD, however, may not be substantially different from the population as a whole. For example, among Caucasians in North America and Northern Europe, (groups which are the least affected by lactase deficiency), this defect is present in 3 to 20 per cent of adults. The prevalence of lactase deficiency is considerably higher in other ethnic groups. This deficiency appears to be an acquired defect which develops in later life, although it may be inherited in some races (241)(277). However, any diffuse disease of the small bowel may also result in a deficiency of the lactase enzyme and impairment of the active transport system in the brush border for the products of lactose breakdown, glucose and galactose. Arvanitakis (12) noted functional and structural small bowel abnormalities in patients with CD, which were associated with reduced levels of numerous jejunal mucosal enzymes including lactase. Bacterial degradation of disaccharidases may also account for the diminished lactase activity accompanying bacterial overgrowth and the blind loop syndrome. Unabsorbed lactose has a marked osmotic effect producing a net flow of water and electrolytes into the bowel lumen. Bacterial fermentation of the sugar in the colon produces toxic metabolites and gases which accentuate the patient's cramping, bloating, borborygmi and diarrhea (241).

The possibility of the presence of a lactase deficiency should be considered in a patient with CD who is bothered by abdominal pain, cramps and watery diarrhea which occur within 30 minutes to an hour of ingesting milk and milk products. Many patients, but not all, will recognize their intolerance (19). Others may needlessly avoid dairy foods. It is important to ascertain whether the patient can tolerate small quantities of dairy products, as many patients can assimilate two or three small servings of milk per day. Others tolerate cheeses and other fermented products with a low lactose content due to bacterial action on lactose. Some patients successfully consume milk treated with Lact-Aid®, a commercial liquid preparation that hydrolyzes lactose (45)(98)(241)(277). Information on the lactose content of various foods is given by Welsh (206) and by the National Dairy Council (1979). Sensitivity to lactose is variable and the amount of lactose that can be consumed without causing symptoms must be determined individually.

Since individual tolerance to lactose is so variable, and because milk and milk products are a major source of a number of nutrients, the extent of lactose malabsorption should be well documented before one assumes lactose intolerance and advises the elimination of lactose-containing foods. While a low lactose diet may obviate the need for more restrictive, nutritionally borderline diets, and at times has achieved dramatic reduction of gastrointestinal symptoms, a diet completely eliminating dairy foods must be prescribed cautiously. To quote LeLeiko (170): "Elimination diets can only be justified if attention to nutritional and metabolic principles assures complete and appropriate nutrition, and then only on a trial basis. The excessive use of elimination diets cannot be justified, since experience suggests that only a few patients will benefit from this form of therapy." Calcium, riboflavin, protein and vitamin D intakes, in particular, may be suboptimal in a diet low in diary products; patients taking Prednisone are particularly at risk since this drug interferes with the metabolism of calcium, protein and vitamin D (109).

The maintenance of adequate nutrient intake in children with IBD is of critical importance to permit normal growth and sexual maturation. In work by Brown et al (45), lactose-malabsorbing children were able to tolerate lactose doses of at least 0.5 g per kg body weight before a rise in breath hydrogen indicated lactose intolerance. In lactose malabsorbing otherwise healthy adults, the amount of lactose ingested at one time that produced symptoms varied from 3 to 96 g (21). About one half of these subjects remained symptom-free with 8 g of lactose, which corresponds to 160 ml of milk. However, in one study (108), 3 out of 20 intolerant subjects experienced symptoms with only 5 g of lactose. Weight gains and nitrogen absorption and retention were significantly greater in lactose-malabsorbing children receiving a simulated milk supplement. Thus, consumption of diary products should be encouraged whenever possible. The patient should receive appropriate nutrient supplements if milk and milk products are not tolerated. These supplements should include calcium, vitamin D, riboflavin and possibly vitamin A. An adequate protein intake should be ensured by increasing the consumption of meat and meat substitutes.

7. Folate

Bowel disorders, particularly those involving the jejunum, are commonly associated with folate deficiency (223). Of 216 inflammatory bowel disease (IBD) patients in a Scandinavian study, 59 percent had a low serum folate and 26 percent had a low red blood cell folate. In the 44 patients with both parameters low, megaloblastic anemia was found in 67 percent (83). Franklin and Rosenberg (93) reported that 63 percent of their patients with CD and ulcerative colitis developed low serum folate, with megaloblastic changes in 10 percent. Dyer et al (78) found low serum folate, low red cell folate and megaloblastic anemia attributable to folate deficiency in 64, 35 and 24 percent, respectively, of CD patients. Hoffbrand and co-workers (135) similarly found a significant incidence of folate deficiency in CD. Comparison among these studies is difficult since there is no standardization in the reference ranges used to assess folate status.

These figures for folate deficiency in IBD are generally higher than the incidence of deficiency in the general populations in Canada and the United States where up to only 25 percent fall into the deficient range (260). Using slightly less demanding standards, 12 percent of the general Canadian population is classified as being at high risk of developing folate deficiency (260). However, these authors had doubts about the validity of the standards used to interpret serum folate levels, and reassessed the maximum prevalence of severe folate deficiency at less than 10 percent based on the finding that liver stores are generally substantial (136).

Folic acid deficiency in CD has been attributed to inadequate dietary intake, malabsorption and excess utilization due to rapid cell turnover during acute inflammation or with accelerated healing (98). Folate is absorbed primarily in the upper jejunum after hydrolysis by conjugases in the mucosal cells (4). Bowel resection should not impair folate absorption if at least 1 to 4 feet of normal jejunum remain (235). However, there is some evidence that CD patients have a disturbance in the acid microclimate of the gut; an abnormally high surface pH dissociates the polyglutamate form of folate and hinders its passive absorption (181). The drug salicylazosulfapyridine (Salazopyrin®) has also been shown to reduce jejunal absorption of folate (93), but this work has not been substantiated by others (100). Swinson et al (257) conclude that sulphasalazine impairs folate absorption but this only becomes significant if other reasons for folate deficiency are also present. The effects of 5-ASA or 4-ASA on folate absorption have not been reported. Elsborg and Larsen (83) found that 23 percent of IBD patients tested malabsorbed folate, though this malabsorption was not related to the site of the disease, nor to maintenance doses of Salazopyrin®. Hoffbrand et al (135) also found malabsorption of folate in 25 percent of those tested. However, not all patients with folate deficiency showed malabsorption. Gerson and Cohen (100) and Morgan et al (201) found normal folate absorption in CD. Decreased intake of folate was suggested as being a major reason for the folate depletion seen in the patients of these studies.

An intake low in fruits and vegetables will predispose to folate deficiency. None of the patients in either Hoffbrand's study (135) or Elsborg and Larsen's (83) consumed more than 200 μg of free folate, while a small proportion of patients in both studies consumed less than 50 μg. An intake of 200 μg of free folate was the Canadian dietary standard in 1975, and the value of 50 μg represents the minimum daily requirement to prevent symptoms of folate deficiency in a healthy adult (124). A previous study conducted at the University of Alberta (130) also revealed a large proportion of patients with CD who had suboptimal intakes of folate, in conjuction with frequent low folate levels in serum. However, the mean folate intake of Canadians in general has been substantially lower than that recommended in Canadian and American dietary standards. The 1983 Recommended Nutrient Intakes for Canadians reflects an effort to re-evaluate the discrepancy between normal and recommended folate intakes and illustrates an attempt to match intakes with the low prevalence of clinical and hematological signs and symptoms of deficiency. As a result, previous recommendations were reduced by approximately half from 400 µg to 220 µg total folate per day for adult males and to 175 µg for adult females. However, megaloblastic changes of folate deficiency anemia are not uncommon in CD and are probably the result of a variety of the above mechanisms present in combination. Furthermore, deficiencies of a single nutrient are probably rare in CD. Biochemical folate deficiency has been found secondary to other nutrient deficiencies including vitamin B_{12}, vitamin C and possibly zinc 131).

From a pathophysiological perspective, the anemia of folate deficiency may be less of a concern in CD than the adverse effects of lack of folate on gut morphology. Folate deficiency leads to impaired cell division and to alterations of protein synthesis. These effects are most noticeable in rapidly growing tissue such as the gut (111). The lesions that are produced in the intestinal epithelium include shortened villi, reduced mitosis, delay in maturation of epithelial cells, and decreased activity of enzymes in the brush border membrane (10)(111). This may help provide the basis by which folate therapy partially alleviates symptoms of malabsorption in patients with tropical sprue (111). However, such a role has not been determined in CD. The final concern of folate status in CD is the role of deficiency in impairing cell-mediated immunity and reducing antibody responses (59). Thus, therapy to normalize folate status in CD has the possibility of improving the overall prognosis through helping to ensure adequate gut function and immune response.

The folate requirement in CD may be increased due to tissue repair, losses through the gut wall or diarrhea, or through drug interference of absorption. This requirement may exceed the amount of folate readily supplied through the diet, particularly if fruits and vegetables are poorly tolerated. Folate supplements may be adviseable. The possibility of associated vitamin B_{12} deficiency should be ruled out (98), as folate supplements will mask the signs and symptoms of deficiency while the nerve damage of a B_{12} deficiency progresses undeterred. Assessment of folate intake may not be sufficient to judge folate status, and measurement of serum or red blood cell folate levels is recommended.

8. Zinc

Zinc deficiency is a well-documented complication of CD. The incidence of low serum zinc levels in patients with CD has been reported at 25% (249), 40% (196) and 46% (91). Low urinary zinc concentrations were found in 36% of these patients, and simultaneous reductions in both serum and urinary zinc levels were detected in 19% of patients (91). The variation in incidence of reported zinc deficiency may be due to limitations in the use of serum zinc to accurately assess zinc status (91) or to differences among the study groups in disease activity, level of steroid therapy, presence of fistulae, or duration or site of disease (91)(196)(249). Poor zinc status has been suggested as having a role in such manifestations of the disease as growth retardation, hypogonadism, anorexia, impaired healing of fissures and fistulae, skin lesions, depressed cell-mediated immunity, impaired taste acuity and depressed dark adaptation (249)(196)(208)(255)(91)(197)(232). Oral zinc therapy in patients with CD has been successful in treating acrodermatitis lesions (196), retinal dysfunction (197) and growth failure and delayed sexual development (232).

Suggested mechanisms for zinc deficiency include malabsorption associated with diarrhea, inflammation or resection, increased requirements, inability to utilize zinc, inadequate dietary zinc, formation of zinc soaps with unabsorbed fatty acids, low serum albumin, and others (255)(91)(232). For example, Sturniolo et al (255) confirmed that zinc absorption was considerably impaired in seven patients with CD. Absorption in the patients ranged from 8-45% compared with 38-75% in the controls. Only two studies have assessed zinc intake in CD. Fleming et al (91) found zinc intake to be surprisingly good in 63 subjects (mean 13.4 ± 1.4 mg/day, range 7 to 27 mg/day), compared to their dietary standard of 15 mg/day. However, dietary zinc did not correlate with serum zinc levels. McClain et al (196) reported that the zinc intake met current dietary standards in 50 out of 52 outpatients with CD. However, 40% of these patients had decreased serum zinc levels. The mechanism of zinc deficiency in CD is most probably multifactorial.

Solomons et al (249) demonstrated impairment of taste sensation in CD patients as compared to controls. Anorexia and growth retardation have been related to taste impairment in Crohn's children with poor zinc status (247). McClain et al (196) narrowed this defect to a diminished acuity of sweetness in zinc deficient CD patients versus those patients not zinc deficient. The high sugar intake in CD noted by many researchers (191)(200)(152)(193)(265)(194) has often been attributed to a zinc-deficiency-induced impairment of taste activity. However, Penny et al (216) found no difference in taste sensitivity in CD patients compared to controls even though serum zinc levels were significantly lower and sugar intake was significantly higher in the patient group. Thus, a cause and effect relationship has yet to be firmly established between zinc status and food habits of patients with CD.

The relevance of a reduced plasma zinc in the pathophysiology of CD relates to potentially impaired cellular immunity and wound healing. Zinc deficiency causes atrophy of the lymphoid tissue and produces abnormalities in both cellular and humoral immunity which can be reversed with zinc repletion (22). If disturbance in the mucosal immune system has an etiological role in inflammatory bowel disease, zinc therapy may be important in the course of the disease. Wound healing is also impaired in zinc deficiency (47). Some mechanisms are discussed by Fernandez-Madrid et al (88), and it has been suggested that collagen is reduced as a part of a generalized impairment in protein synthesis. Other studies suggest that interference with the synthesis of DNA due to zinc deficiency is important in preventing fibroblast proliferation. Wound healing appears to be accelerated by adding zinc to the diet, but only in those patients who have a low serum zinc concentration (273).

Diarrhea can be a clinical manifestation of zinc deficiency, but many patients said to be zinc deficient may have diarrhea from other causes. The zinc deficiency, then, could be secondary to the diarrhea, since stool is the major route of zinc excretion (92). However, zinc deficiency has been associated with degenerative changes in enterocytes and damage to microvilli in the small intestine of rats (82). Abnormalities in Paneth cells of the epithelium have also been produced in rats fed a zinc deficient diet. A similar proliferation of inclusion bodies in the Paneth cells has been shown to disappear after oral zinc therapy in acrodermatitis enteropathica, a rare familial disease with impaired zinc absorption (92). One can speculate on a primary role for zinc in maintaining normal gut structure and function.

Naveh et al (207) believe that the healing of injured intestinal mucosa is, in many respects, analogous to such processes as wound healing, and the epithelialization of burns, and may be similarly delayed in zinc deficient patients. The situation may be complicated if protracted diarrhea and poor zinc status result in immunodeficiency and infections. Thus, an intimate role for zinc may be visualized for improving the clinical status of patients with CD. Elmes and co-workers (81) have reported a low serum zinc level in six severely ill non-responsive celiac patients zinc replacement therapy resulted in a sustained improvement in general well-being, intestinal absorptive function and nutritional status in all six. However, Jones and Peters (149) were unable to produce a significant change in clinical status or jejunal morphology despite normalization of plasma zinc levels after eight weeks of oral zinc therapy in three celiacs. The jejunal maltase, sucrase and lactase activities were nonetheless improved, possibly through brush border membrane stabilization by zinc ions. Accordingly, well-controlled trials of zinc therapy in patients with

CD are needed to assess the possible benefits of zinc in the etiology of the disease process and the complications encountered in this disease.

V. Assessing the Effects of Nutritional Counselling and Supplementation

In the present study, the effects of nutritional counselling and supplementation are being assessed at a number of levels; improvements are sought in nutrient intake, anthropometric status, laboratory parameters and clinical well-being. The following sections will discuss the rationale for the selection of the standards and criteria used in determining the initial nutrient status of patients and subsequent change over time.

1. Assessment of Nutrient Intake

Dietary assessment is critical to the individualization of the patient's nutritional care plan. The adequacy of the nutrient intake of a subject is typically compared to the current dietary intake standards appropriate for the sex and age of the individual. However, the standards to which the assessed intake is compared apply to the normal, healthy population, not to the individual who may have decreased needs due to small stature or low energy output, or increased requirements due to chronic disease or medication. Methods of estimating nutrient intake are numerous: food frequency questionnaires, food records, dietary recalls and variations thereof each have their own advantages and disadvantages. Interpretation of nutrient intake estimates must take these limitations into consideration.

The food frequency method asks questions about the frequency of eating particular foods over a certain length of time, from a week up to a year. This method may be used to assess the composition or quality of the diet, but cannot be used to predict the intake of individual nutrients. Hunt et al (139) found that the mean estimates of energy and carbohydrate intake were similar when comparing the results of a food frequency questionnaire with the mean values of five 24-hour dietary recalls, but data on other nutrients were from 6 to 88% greater with the food frequency method. Furthermore, the food frequency questionnaire was found to provide a more accurate estimate of the intake of the major components of a meal, such as meat, compared to the consumption of smaller amounts of foods, such as nuts (205). Finally, the food frequency questionnaire was not found to be valid for the determination of the food intake of an individual (205). The food frequency method may be a useful adjunct to the 24-hour dietary recall method in an attempt to obtain a more representative food intake.

A food record is kept for a specified period of time, typically one to seven days. The intake may be simply recorded, or weighed and recorded. From this record can be calculated a relatively accurate account of the nutrient intake for those particular days. A food record eliminates error due to memory, but requires greater cooperation and motivation on the part of the individual. A major drawback to this method is that individuals may alter their food habits during the period of recording their intake in order to fit their preconceived notion of what they should consume (101).

The dietary recall method is frequently chosen for studies involving large groups. The 24-hour recall method was used in the Ten-State Nutrition Survey (1969-1970), the Nutrition Canada Survey (1970-1972) and the U.S. Health and Nutritional Examination Survey (1971-1974). Criticisms of this method concern whether an individual can accurately remember his past intake and whether the intake of one or more selected days is actually representative of an individual's habitual intake. In particular, certain nutrients such as vitamins A and C have considerable day-to-day variation in their intake (190). While this method has limitations in supplying information at the level of the individual, it is widely accepted that when the method is applied to many persons, the average of the 24-hour recalls may properly depict the intake of the group (159). Young et al (289) state that the 24-hour recall provides a suitable method for getting the average intake of groups of 50 or more subjects, as long as a 10% error is acceptable. Furthermore, Gersovitz et al (101) found the 24-hour recall to be as accurate as, and more convenient than, the 7-day record for group comparisons. They also noted that the recall method underestimated extremes in intake, so that while this method would seldom indicate a difference between population groups where none existed (false positive effect), there was danger of failing to detect an actual difference between groups (false negative effect).

While surveys of the dietary intakes of groups of persons can be of value, such surveys provide no information on individuals who may have very different diets and/or nutritional needs than the average of the group surveyed. When the 24-hour recall has been repeated on individuals, the correlation of nutrient intakes is poor (159). In fact, within-person variability is as large as between-person variability for many nutrients. Marr (190) assessed the question of day-to-day repeatability in surveys on individuals and attempted to determine the shortest period for which it is necessary to record dietary intakes. He classified the individual's intakes in terms of thirds of the total distribution of the group (ie. lowest, middle and highest third). By way of example, he used a previous study where the between-person standard deviation was 400 calories and the within-person standard deviation was 370 calories. With this level of variation he found that a one-day weighed food record would correctly classify 65% of the individuals for calories, but 5% would be grossly misclassified, i.e.their "true" position being in the opposite third of the distribution. A two-day weighed food record would correctly classify 77% of persons with 1.5% grossly misclassified, a three-day weighed food record would correctly classify 82% of subjects with 0.5% misclassified. Other authors have advocated that four-day records (56) or seven-day records (1) are best to determine the habitual intake of an individual. Energy and protein have been found to be estimated with the highest precision, while vitamins A and C show extreme fluctuation (190).

The 48-hour recall used in the present study has been used previously (244)(130), and is an attempt to minimize error due to day-to-day variation while not unduly taxing the memory of the patient. However, research has not been done to confirm whether a 48-hour recall provides a more representative intake than a single 24-hour recall, or two successive 24-hour recalls.

Accuracy of the various dietary assessment methods, then, is limited by intra-individual variation, by the memory and cooperation of the subject, and by the persistence of the interviewer (1). Some methods are time consuming or unsuitable for large numbers of subjects. A strong sex difference and day of the week effect (20), as well as seasonal variation (190)(159), have been found in reporting absolute nutrient intakes. Furthermore, the limitations of food composition tables must be recognized. The nutrient composition of food varies with the geographical region and the method of handling and processing. Finally, information regarding certain nutrients and trace elements is incomplete for some foods (159).

Standards for interpreting the data collected by these methods also have limitations. Like dietary assessment methods, the standards with which to compare the estimate of nutrient intake are only valid for groups within a population rather than for the individual. Recommended intake tables such as the 1983 Recommended Nutrient Intakes for Canadians (RNI) are set to ensure against the development of deficiency in a normal healthy population. Thus the RNI exceeds the requirements of the majority of individuals within the population. The RNI allowance is set at about two standard deviations above the mean requirement for nutrients, and at the mean requirement for energy (158). Therefore, a person who consumes less than the RNI may not develop a deficiency, but with low intakes over a period of time the risk of developing deficiency increases. On the other hand, the application of current standards to an unhealthy population, as in the present study, can be successful only if it is realized that nutrient requirements are probably increased in illness and the standard may, in fact, constitute the minimum amount of a nutrient which will keep the patient in balance.

In many studies conducted on individuals, a major purpose of collecting food consumption data is to classify the individuals with respect to the distribution of nutrients within the group. Various indices have been suggested for reporting nutrient adequacy and for monitoring changes in food intake as a result of dietary intervention. Marr (190), as noted previously, classified individuals into tertiles of the distribution of the group. Using the American Recommended Dietary Allowance tables (RDA), Bowering and colleagues (39) reasoned that because the RDA is a recommendation for groups of people rather than specific nutrient intakes which will prevent deficiency, it seemed appropriate to use a value of less than 100% RDA as a standard comparison. These workers examined changes in the proportion of subjects meeting 2/3 RDA for calories, calcium and vitamin C. They also expressed dietary adequacy as the proportion of nine nutrients (calories, calcium, iron, vitamins A and C, two B vitamins, and protein) for which intake met 2/3 RDA, as well as comparing the percent of subjects meeting 2/3 RDA for four or more nutrients. In a subsequent paper (40), this group found that a total food score (the sum of the intakes for the individual food groups) and total energy intake were also effective indices in monitoring changes occuring with dietary intervention. Other workers (146) have likewise determined that dietary deficiencies can be more easily examined when data are presented as nutritional profiles; they presented nutrient intakes in a series of intervals, each 15% of RDA, from 100 to 55% of RDA.

Hansen and Wyse (114) have discussed expressing the nutrient composition of diets, foods and even the nutrient intake standards on the basis of nutrient density (nutrients per 1000 kcal). This common basis allows direct comparison between two parameters such as the diets of males and females. This method of expression has been shown to remove the day of the week variation found in females (20). Diets and intakes can thus be assessed with respect to their ability to meet intake standards in terms of the energy provided.

In summary, each method of collecting food consumption data contains sources of error which are very difficult to eliminate. In deciding which method to use, the purpose of the study must be clearly defined. Regardless of the chosen method, interpretation of the resulting nutrient intake data must be undertaken cautiously. It should be remembered that an adequate nutrient intake, i.e one meeting the RNI, should not be interpreted as equivalent to an adequate nutritional status. This point is particularly important in patient populations. Kerr and associates (158) found that the predictive value of nutrition survey data to laboratory indices in the HANES study was poor. Thus, anthropometric, laboratory and clinical assessment of nutritional status are also necessary to determine if the food intake is appropriate for that individual.

2. Anthropometric Assessment

The usefulness of anthropometric assessment is based on evidence that the body, when faced with nutritional restriction, utilizes its nutritional reserves stored in the form of skeletal muscle protein, visceral protein and fat (96). Sub-standard triceps skin-fold thickness (TSF), arm muscle circumference (AMC) and weight for height have been shown to have functional consequences, i.e. increased morbidity and/or mortality, and immunoincompetence (276)(53)(120)(31). However, while these measurements are the simplest, most direct and perhaps most specific of the common methods of screening for protein-energy malnutrition (107), their sensitivity and current standards for comparison have been criticized and critically reviewed (221)(107)(32)(96). The use and interpretation of anthropometric measurements in CD will now be described.

The TSF thickness is a convenient measure of a patient's subcutaneous fat stores, and can be considered a reliable index of the body's energy stores (107). Body weight-for-height and mid-arm circumference (MAC) are also used frequently to assess "fatness" but it should be remembered that they are composite measures reflecting both fat and muscle mass. Further, weight is an unreliable index of protein-energy nutriture in the presence of disease or therapy leading to fluid retention. In these circumstances, MAC and TSF thickness are often a better index, because the upper arm is usually relatively free of edema (34). In CD, the use of Prednisone to control symptoms may contribute to rapid weight gain. This increase in weight is thought to be due to improved symptoms and appetite, or to fluid retention, and is not necessarily correlated with improved nutritional status. The literature does not describe if the fluid retention of steroid therapy spares the upper arm as does edema. The fluid distribution may follow an individual pattern. If the arm is not spared, measures of body composition other than anthropometrics would be required to assess energy status such as multiple isotope dilution.

A profile of tests, measurements and derivations has been developed to assess the static, dynamic and functional aspects of protein status and lean body mass. This profile includes AMC or muscle area, total body ^{40}K, nitrogen balance, skin antigen reactivity, creatinine-height index, serum albumin, serum transferrin and lymphocyte count (96)(267)(33). It is assumed that arm muscle size reflects the reserve of muscle protein while the levels of circulating protein such as transferrin or albumin, indicate the visceral protein status (96).

Rich (221) addressed the question of whether subtle changes in the lean body mass of an individual are detectable using conventional methods of anthropometric assessment. He noted that the standard error of, for example, the TSF was 1.5 mm, equivalent to 1.9 kg of total body fat in the example patient described. Furthermore, even if observer accuracy was assumed, Rich cites that three or four TSF measurements still have a standard error of 5% or 2.7 kg of fat in the same example patient. He calculated similar figures for the AMC and concluded that this magnitude of inherent measurement error was sufficient to mask the more subtle changes in body composition. Hall et al (110) assessed the problem of measurement variance when several observers are performing anthropometry. They illustrated that a change in AMC of up to 2.68 cm was attributable to inter-observer variation. Collins et al (60) found anthropometrics to be a reliable assessment of protein status only when used with larger groups of patients. For example, for 100 patients, the 95% confidence limits were calculated to be ± 30 g nitrogen or 188 g protein. This is equivalent to 2% of the total body protein. This magnitude of variance makes it inappropriate to use AMC for assessing the individual in a single measurement, where 95% confidence limits were calculated to be ± 300 g nitrogen or 1875 g protein. Furthermore, anthropometrics were not found to be reliable in following changes in body nitrogen in individual patients over a short period of time, as correlations between the two parameters were poor. Thus, anthropometrics should not be the sole basis for determining nutritional status in a patient.

Various anthropometric norms have been used in the assessment of nutritional status. Standards proposed by Jelliffe (142), developed for use in underdeveloped countries, have been thought to underestimate the average measurements of most Americans (107). Data of the Ten-State Nutrition Survey (95) are not representative of the total U.S. population since the survey was composed chiefly of low-income, minority group individuals (107). Furthermore, the study did not give information for subjects older than 44 years of age. Data of the U.S. Health and Nutrition Examination Survey (HANES I), collected during 1971 to 1974, has been used to derive the most representative American standards. Just recently, standards for Canada have been made available, based on the Nutrition Canada Survey (1970-72). However, Metropolitan Life Insurance data continue to be used widely, providing the only body weight standards that relate to mortality (32).

Various authors have addressed themselves to the misclassification of patients using current methods. Gray and Gray

(107) state that the use of the same percentages to indicate depletion for all anthropometric measurements (as suggested by Blackburn et al, 33) fails to take into account that the normal variation for some measurements is greater than for others. For example, 60% of the standard for AMC indicates a more severe depletion than 60% of the standard for TSF. These authors suggest an alternate method of interpretation based on the use of percentile distribution, where measurements between the 5th and 15th percentiles could be considered at risk of becoming depleted, and below the 5th percentile would be evidence of depletion. Frisancho (96) proposes the use of fat and muscle area rather than circumference. This suggestion is based on the theory that it takes more fat to cover a larger limb with a given thickness of subcutaneous fat than it does to cover a smaller limb with comparable thickness. He illustrates that estimates of TSF thickness and muscle circumference underestimate the magnitude of age-related changes in upper arm fat and muscle. It remains to be seen if these suggested parameters will come into widespread use. Himes et al (129) found fat area to be a better estimate of the weight of fat in the body, but equivalent to TSF in assessing the percentage of body fat.

The anthropometric status of patients with CD has received little attention in the literature. Harries et al (115) have found that anthropometric measurements were valuable in identifying those patients with inflammatory bowel disease who were most likely to have clinical features of malnutrition. All anthropometric measurements were significantly reduced in 106 out-patients with CD compared with controls and ulcerative colitis patients. Furthermore, significantly more patients with CD were also below the 90% ideal for weight and anthropometric parameters. The proportions of CD patients below 90% for ideal body weight, MAC, AMC and TSF thickness were 20%, 37%, 35% and 51%, respectively. Corresponding proportions in the control group were 3%, 11% 19% and 22%, respectively. The poorest anthropometric status was associated with diffuse CD in the small bowel, which also correlated with lower serum albumin and pre-albumin concentrations. Active CD (CDAI greater than 150) was associated with significant decreases in TSF thickness and serum albumin levels. Steroid therapy was associated with reduced body weight and AMC. Previous extensive bowel resections were associated with reduced TSF thickness and lower serum albumin. Duration of symptoms had no effect on measurements. The authors noted that the fact that patients with small bowel disease had the lowest measurements supports the view that malabsorption is important in creating nutritional depletion, and is additive to the effects of anorexia and active inflammation. They also cautioned that anthropometry alone cannot define nutritional status, but is useful to help identify the risk of malnutrition in patients.

Despite the widespread use of anthropometry in nutritional assessment, the need for more sensitive determinations of protein-energy status has been illustrated in the study by Baker et al (14). These workers found clinical assessment to be as reliable a method of nutritional evaluation as objective measurements, which included percent ideal weight and lean body weight, and percentage body fat. However, edematous patients may appear outwardly healthy and anthropometric measurements would detect underlying nutritional depletion provided measurements other than on the arm were done, e.g.

in the sub-scapular region. In addition, a numerical description of nutritional status is often desirable in research and in patient evaluation. The limitations of measurement error and individual differences in the distribution of body fat and muscle should be taken into consideration (107). Despite these limitations, anthropometry remains a relatively reliable, specific, non-invasive technique of nutritional assessment.

3. Laboratory tests for the assessment of nutritional status

Biochemical measurements indicate the state of body metabolism at a given point in time, and represent the most objective assessment of the nutritional status of an individual (233). Various nutrient assays may provide specific information at three levels: 1) serum levels of nutrients are often a sensitive reflection of recent dietary intake but may not provide information on the long-term nutritional status; 2) tissue analyses may provide evidence of longer-term dietary deficiency and depletion of body stores which is of prognostic but not necessarily functional value; finally, 3) functional biochemical measurements (such as metabolite formation or enzyme function tests) detect metabolic abnormalities and can provide early indications of subclinical deficiency states. Serum assays, though the most difficult to interpret, are often the simplest technically to perform, and it is assumed that continued nutrient levels at the critical end of the reference range may eventually lead to metabolic abnormalities.

It is important to recognize that there are certain limitations to all biochemical measurements, and their interpretation must take into account the level of technical difficulty, the degree of sensitivity and specificity, and intra- and inter-individual variation. Inter-laboratory variation must be considered when comparing test results from various sources. The use of fasted subjects (blood samples taken in the morning before breakfast) will correct some of the fluctuations of nutrients in the blood which result from recent dietary intake and differences in the time of day. Unlike nutrient intake estimates, within-individual variation of lab results is generally much less than between-individual variance, facilitating statistical analyses. Reference ranges, which are categorized according to age and sex, where appropriate, define cut-off points for determining risk of deficiency or excess. These limits, though based on current knowledge, may be arbitrarily designated and subject to change as newer methods and information become available. Reference ranges must be determined by each individual laboratory in order for the ranges to be appropriate for the methodology used and for the indigenous population. Standardization of methods and reagents has been achieved for some tests such as serum protein or calcium, but other methods involving enzyme or radio-immunoassay procedures produce fluctuations from lab to lab, depending on the purity of reagents such as antibody or enzyme preparations.

No single test or measurement can provide an accurate nutritional evaluation, so a battery of parameters is usually assessed. The tests described in the following section relate to the nutritional problems of patients with CD. The validity of these tests in the laboratory assessment of nutritional status in CD will be discussed.

A. Tests of protein status

Serum albumin and transferrin levels are generally lowered in the presence of stress, such as inflammation (221). These levels are reliable indices for estimating protein status (233), except in patients with concurrent chronic hepatic or kidney disease (278). Transferrin, with its shorter half-life, reflects nutritional depletion and repletion more rapidly than does albumin (31), although both proteins are preserved in the normal range until quite late in the development of deficiency. Significant visceral protein depletion is indicated when the serum albumin is less than 3.0 g per 100 ml; changes characteristic of malnutrition, including anergy, edema, sepsis and immunocompetence, can be expected when this lower limit is exceeded (30)(35). Baker et al (14) cautioned against including both albumin and transferrin parameters in a single index of nutritional status, as many have suggested (53)(33) since they are highly correlated. Total serum protein levels lack sensitivity and specificity, so are of little value as an estimate of protein status (233). Total protein levels rise in inflammation due to increased levels of immunoglobulins. This would limit their use in CD.

Nitrogen is the primary component that differentiates protein from other nutritional moieties. Since protein status reflects the overall state of nutrition, nitrogen balance is often employed as an index of protein status (278). Blackburn et al (33) suggest that a measurement of nitrogen balance is also useful in documenting the effectiveness of nutritional therapy. The formula for nitrogen balance is: (183);

$$\text{nitrogen balance} = \frac{\text{protein intake(g/day)}}{6.25} - \text{urinary urea nitrogen (g/day)} + 4$$

Since infection or other stress increases the proportion of the energy expenditure that is provided by amino acid oxidation, the 24-hour urinary urea nitrogen excretion may also be used to estimate the actual metabolic expenditure and to detect a hypermetabolic state in patients on a protein-free or low-protein diet (33)(31). However, urinary urea nitrogen levels are related not only to muscle mass but to age, exercise, sex, diet and renal function, and must be interpreted with caution (150). Furthermore, non-urinary nitrogen losses can be significant in patients with diarrhea (33), as in CD.

The creatinine height index (CHI) is an effective measure of muscle mass. Urinary creatinine varies primarily with the extent of skeletal muscle catabolism (33). The CHI is calculated as follows:

$$\text{CHI} = \frac{\text{measured urinary creatinine/24 hours}}{\text{ideal urinary creatinine/24 hours}} \text{ X } 100$$

where ideal urinary creatinine varies with body height. Urinary creatinine cannot be used to assess muscle mass in renal insufficiency but, unlike urinary urea nitrogen, it is not affected by diet, moderate exercise or diarrhea (150)(274). Reliability of the CHI, as with the nitrogen balance calculation, depends upon the accuracy of the urine collection over the 24-hour period.

Many parameters for nutritional assessment focus on protein status; Winborn et al (284) have suggested that this emphasis is because it is the patient's protein status which affects his response to stress, because protein (and energy) requirements are the most difficult to meet in a patient, and because protein deficiency is corrected more slowly than vitamin or mineral deficiencies. Seltzer et al (236) have proposed that since serum albumin and total lymphocyte count relate to morbidity and mortality, these variables may be used for rapid assessment in the critically ill when a more complete profile of protein status cannot be calculated due to time limitations. The use of these variables in CD must be made cautiously as protein losses through the inflammed gut and the use of glucocorticosteroid therapy would interfere with serum albumin and total lymphocyte count, respectively, regardless of nutritional status.

B. Tests for anemia

1) Iron

The iron-binding capacity of the serum permits the distinction of nutritional deficiency from iron deficits due to other causes such as infectious, inflammatory or neoplastic diseases (233). Uncomplicated iron deficiency produces a rise in iron-binding capacity and a fall in serum iron. The most sensitive parameter in screening for iron deficiency is the ratio of serum iron to iron-binding capacity, the transferrin saturation (61). This measurement is sensitive though not without limitations. The method is time-consuming and subject to wide diurnal variations in normal individuals. Also, a decline in transferrin saturation can occur in relatively mild or transient infection and inflammation and, therefore, is not specific for iron deficiency (61).

Another sensitive parameter of iron status is the serum ferritin level, the major intracellular form of iron, which correlates well with body iron stores (61). Serum ferritin falls in iron deficiency but rises with inflammation (176). Thus in CD a very wide distribution of values may be found, and which will be difficult to interpret. The increased serum ferritin in CD patients with inflammation is likely related to the ferritin acting as an acute phase reactant, fluctuating with the activity of the patient's disease, and thereby possibly obscuring an early or latent iron deficiency. Thomson et al (262) noted that a serum ferritin less than 18 ng/ml indicated with excellent specificity (predictive value of 100%) that iron stores were depleted in patients with inflammatory bowel disease. However, this measurement was found to have a low sensitivity in these patients. In addition, the precision of ferritin determinations is limited when extremely low levels of iron are present.

Hemoglobin and hematocrit measurements are not specific for iron deficiency anemia (233), and are the least sensitive indices of iron deficiency, falling only after iron stores have been depleted, and when red cell production is impaired (61). Graitcer et al (105) found that hemoglobin tests detected higher rates of iron deficiency anemia (i.e. were more sensitive) than hematocrit tests, when using commonly assumed "equivalent" cut-offs for each parameter.

ii) Folate and vitamin B_{12}

Serum folate, red blood cell folate and, less specifically, mean corpuscular volume (MCV) may be determined to assess short-term, long-term and functional folate status, respectively. Serum folate levels are the most commonly performed, are technically easy, are sensitive, and provide an early assessment of folate deficiency. Unfortunately serum folate levels do not specify the degree of deficiency and may simply indicate a recent low intake of folic acid (233).

Red cell folate levels are regarded as a more accurate, less variable quantitative index of the severity of folate deficiency than is serum folate (233). Red cell folate levels correspond closely with liver stores (4). The procedure for determining red cell folate is an involved task in that both serum and whole blood folate levels must be measured, and the folate level in the red cells calculated on the basis of the hematocrit value (233). Red cell folate determinations are dependent upon a reliable cell preparation. This introduces another source of error, so that the precision of this test is not as high as for serum estimates, especially when the RBC folate levels are low. A low folate level in both serum and red blood cells is strong evidence that a folate deficiency exists, and there will probably be associated bone marrow morphology and/or hematological changes (233). The low end of the ideal reference range for serum folate varies considerably, from 1.7 ng/ml (University of Alberta Hospital) to 3.0 ng/ml (4), while the lower limit of red cell folate is most commonly set at 140 ng/ml.

A functional assessment of folate status is available with a MCV determination, where macrocytic changes indicate impaired erythropoiesis. However, low red cell folate levels may result secondarily from a deficiency of vitamin B_{12} (4) or iron (24), and a high MCV may be associated with many causes, including a folate and/or vitamin B_{12} deficiency. In addition, the predominantly microcytic structure of the red blood cells in a possible associated iron deficiency anemia may conceal the macrocytes of a folate deficiency (67). Thus, iron, folate and vitamin B_{12} indices are all necessary to determine the cause of anemia in a patient at risk of developing multiple deficiencies.

The biochemical procedures to evaluate vitamin B_{12} status are designed to establish whether a deficiency exists. Red blood cell or leukocyte determinations of vitamin B_{12} do not appear to provide any advantages over serum as an index of vitamin B_{12} status. Low serum B_{12} levels accurately reflect low body contents of the vitamin (233). Once a deficiency is detected, absorption tests can be employed to determine whether the low serum B_{12} level is the result of lack of intrinsic factors, or malabsorption, or to a nutritional deficiency of vitamin B_{12}. Pernicious anemia can be readily diagnosed by the Schilling test where measurements are taken of the absorption of orally administered radiolabelled vitamin B_{12} given first without and then with intrinsic factor. In CD, ileal resection, decreased intrinsic factor, and bacterial overgrowth may reduce the absorption of vitamin B_{12} (78)(89).

Folate and vitamin B_{12} metabolisms are closely interrelated. Vitamin B_{12} is needed to convert the circulating form of folate into the proper form for uptake and storage by the red blood cells (4). Deficiencies of each vitamin cause morphologically identical macrocytic changes, obscurring the cause of anemia. Serum levels of each of folate and vitamin B_{12} should be measured when multiple nutrient deficiencies are possible.

C. Tests of vitamin A status

Vitamin A status is assessed through serum levels of vitamin A and carotene. There is no readily determined biochemical measurement of metabolic derangement due to vitamin A deficiency. Methods to determine night blindness and impaired dark adaptation are technically difficult and unspecific (233). Serum vitamin A is an accepted measure of dietary intake and hepatic stores of vitamin A. Serum levels below 300 ug/L indicate deficient intake of several months' duration, and stores that are in the process of being depleted. Symptoms of vitamin A deficiency occur at serum levels of 100ug/L or less (233). Depressed serum vitamin A levels may be encountered unrelated to impaired intake, in patients with fever, chronic infection, liver disease and celiac sprue (233). Serum carotene levels also vary with dietary intake, and low serum carotene levels must therefore be interpreted with caution. A low serum carotene may simply indicate a low carotene consumption, while preformed vitamin A intake and liver stores remain satisfactory. Secondly, a low serum carotene could reflect increased efficiency by the individual of the conversion of B-carotene to retinol and its absorption in the intestinal mucosa (36). The measurement of serum carotene may be useful if incorporated into an initial screening for malabsorption. A low serum level of carotene, despite adequate carotene intake, is a sensitive indicator of absorptive problems (253).

D. Tests of vitamin C status

A functional biochemical procedure relating to vitamin C status is not yet available. Vitamin C status is determined by serum and leukocyte levels of vitamin C. Serum levels reflect recent intake of vitamin C (233), whereas vitamin C levels in leukocytes are a closer measure of tissue saturation with vitamin C (266). Serum vitamin C levels are reduced in chronic inflammatory diseases, in acute and chronic infections, in cigarette smokers and in women taking oral contraceptives (233). The nutritional significance of these low serum levels remains largely unknown. Leukocyte ascorbate levels fall more slowly than serum levels, and leukocyte ascorbate levels below 7 mg/dl are most closely associated with the onset of signs of scurvy. However, determination of the ascorbate content of white blood cells is technically difficult, requires a relatively large sample of blood, and needs careful handling due to the instability of the vitamin. As with red blood cell folate determinations, a reliable cell preparation is required, and precision is poor at low levels of leukocyte vitamin C. Leukocyte assessments are, therefore, not practical for routine use in nutrition surveys (233). Serum levels of vitamin C provide a useful alternate to the leukocyte measurement. Prolonged low serum levels indicate a risk of developing symptoms of ascorbate deficiency. Serum vitamin C levels are also sensitive indicators of nutritional repletion.

E. Tests of mineral status

The measurement of various minerals, including calcium, phosphorus, magnesium, zinc and copper, should accompany a complete nutritional assessment. Low serum calcium and phosphorus concentrations in conjunction with an elevated alkaline phosphatase may be interpreted as evidence of a bone disorder, specifically osteomalacia. These abnormalities also provide an indirect measure of poor vitamin D status, caused, for example, by steatorrhea (150). Blood levels of calcium, phosphorus and magnesium are normally controlled by highly developed homeostatic systems so that, should they vary outside the normal range, one might suspect pathological problems before dietary inadequacies (233). For example, low serum magnesium levels are frequently associated with malabsorption, prolonged diarrhea and fistulae (150), all typical of CD.

Low serum zinc (255) and copper (266) levels are observed in hypoproteinemia associated with malnutrition or malabsorption. Low serum zinc levels in CD have been correlated with the sub-optimal concentrations of serum albumin, the major zinc-binding protein (91). However, acute and chronic inflammation may simultaneously increase serum copper and decrease serum zinc levels. Fleming et al (91) proposes the use of urinary levels of these trace elements to more accurately assess their status in CD.

F. Tests for malabsorption

The presence of steatorrhea should be ascertained in CD since the following chain of events may occur: unabsorbed fat binds with dietary calcium in the lumen and calcium absorption is decreased. Excretion of calcium in the urine is also lowered. Due to the formation of a calcium/fat soap, less calcium is available in the lumen to bind with, and render insoluble, dietary oxalate. This results in enhanced oxalate absorption, hyperoxaluria and possibly renal oxalate stones. Stauffer (254) has observed the benefits of a high calcium intake in suppressing oxalate secretion to normal levels in patients with mild to moderate steatorrhea. Urinary calcium and oxalate determinations are useful in assessing the etiology of kidney stones common in CD.

In the patient with CD, 72-hour stool collections should be obtained to provide information on fecal weight, fat and bile acids. For stool fat measurements, the fat content of the diet must be documented. Often a standard 100 g per day fat diet is prescribed for the days preceding and during the collection. The completeness of a 48- or 72-hour stool collection must always be ascertained. Analyses of random specimens or 24-hour stool collections are not recommended since the results are subject to errors due to the wide variation in the bulk content of diets (266).

The presence of excessive bile acids in the stool is common in patients with CD (87). With the loss of the ileal carriers for the active intestinal reabsorption of bile acids, excessive bile acids enter the colon where they stimulate cyclic AMP. This results in a secretory diarrhea. If a larger segment of ileum is diseased or resected, the liver may be unable to continue to increase its secretion of bile acids. As a result, the concentration of bile acids in the upper intestine may fall below the level critical for the formation of micelles. Without the formation of micelles, steatorrhea will develop. Thus stool collections and analysis for fat and bile acids will assist to determine whether the diarrhea in the patient with CD is due to malabsorption of bile acids, or malabsorption of fat. This is an important distinction, since the former is treated with a bile acid binding agent (cholestyramine, Questran®), and the steatorrhea is treated with a modification in the type or amount of fat in the diet.

Assessment of vitamin K status provides a functional assessment of the degree of fat malabsorption. The length of time for blood to clot is measured, the principle being that vitamin K deficiency interferes with the production of various clotting factors resulting in prolonged blood clotting time; the prothrombin factor II is measured specifically in this test (233). A relatively large amount of blood is required for measurement of clotting time and the test must begin shortly after the blood is withdrawn from the patient. While this test assesses functional complications resulting from fat malabsorption it does not provide an early indication of steatorrhea.

G. Tests of immune function

In a previous section (Diet and Immune Function) were reviewed the reports indicating that immunocompetence is a sensitive and functional barometer of nutritional status, as well as possibly being an index of patient morbidity and mortality. Chandra and Scrimshaw (58) have suggested a number of tests of immunity that can be used as adjunct parameters of nutritional assessment. These include measurements of complement components, the evaluation of cutaneous delayed hypersensitivity, T-lymphocyte count, the assay of secretory IgA, the measurement of the microbicidal capacity of neutrophils, and the assessment of terminal deoxynucleotidyl transferase concentration. An estimate of immune function may also be obtained from the total lymphocyte count; a count of less than 1200 to 1500/mm^3 suggests impaired cell mediated immunity (276). However, many disease states and medications can also impair immune function (31). For example, prednisone used in the treatment of CD may suppress the lymphocyte count.

In conclusion, it should be kept in mind that laboratory assessment of nutritional status represents a multiparametric profile, and the interpretation of laboratory data should take into consideration the limitations of each individual method employed as well as the specifics of the patients' individual condition.

4. Clinical Assessment: Crohn's Disease Activity Indices

A number of indices have been developed in an attempt to give a numerical reflection of the clinical severity of CD. The most widely known is the Crohn's Disease Activity Index (CDAI) designed for the United States National Cooperative Crohn's Disease Study (26). There have been several subsequent modifications of this index, including that of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD), sometimes referred to as the Oxford system (70), that of the European Crohn's Disease Study (186), the Dutch Index (269), and modifications by Harvey and Bradshaw (122), Burnham et al (48), Andre et al (9), and Cooke and Prior (63).

Calculation of the CDAI is outlined on pages 5 and 6 of Appendix I. Index values of 150 and below are associated with quiescent disease. Values above 150 indicate moderately active disease, and those above 450 are associated with severe disease. In developing the CDAI, the study group originally selected 18 variables suspected as being indicators of disease activity. Multiple regression with stepwise deletion eliminated all but eight variables which correlated most closely with the attending physician's over-all evaluation of the patient's status and the assessment of the change in the patient's clinical status in comparison with the previous visit. Coefficients for each variable were computed to account for the differences in contribution of that variable to predicting the physician's evaluation.

Limitations to the CDAI are numerous and include: 1) the heavily-weighted subjective component (severity of pain, sense of well-being) which renders it particularly unsuitable for the assessment of drug therapy with euphoriant effects such as Prednisone (134); 2) the lack of reference to past resections or therapy other than antidiarrheal agents; 3) interference of the weight variable by corticosteroid therapy, irrespective of disease activity; 4) the possibility of diarrhea and abdominal mass unrelated to the disease process; 5) and the wide range of values (from slightly negative to over 600) which may interfere with statistical analysis. It has been suggested that the CDAI is too cumbersome for practical use as a patient diary card is required for the preceding week, and a hand calculator may be needed to compute the final score (134). Finally, Andre et al (9), among others, have suggested the inclusion of laboratory parameters other than hematocrit, which they did not find to correlate with disease activity.

One modification of the CDAI, as proposed by Harvey and Bradshaw (122) and amended by the Organisation Mondiale de Gastroenterologie, assesses 5 aspects over one day only. Their index correlates well with the CDAI and has a range of 0 to 21:

1. general well-being on a score of 0 to 4 (0 being perfectly healthy, 4 being very sick)
2. abdominal pain on a score of 0 to 3 (0 being no pain, 3 being severe pain)

3. bowel actions on a score of 0 to 5 (0 being a normal bowel habit, 5 implying 10 or more stools per day, or, alternately, number of liquid stools per day)
4. abdominal mass on a score of 0 to 3 (0 being no mass, 3 being a definite tender mass)
5. complications both local and systematic (score 1 for each).

The Oxford or IOIBD system (70), also a one-day index, gives a score of 1 for the presence of each of the following features:

1. abdominal pain
2. more than 6 bowel motions per day, or blood and mucus in the motions
3. anal complications
4. fistulae
5. other complications
6. presence of a mass
7. presence of wasting or emaciation
8. a temperature greater than 38°C
9. the presence of abdominal tenderness
10. a hemoglobin below 10 g/dl

The European system (186) is similar to the Oxford except that it includes the presence of a low serum albumin as a further index of severity.

The Dutch Activity Index (269) is a combined clinical and laboratory index, calculated as follows:

Albumin (g/L)	X	-5.48
ESR (mm/h)	X	0.29
Body mass index (Quetelet) $\frac{\text{weight (kg) X 10}}{H^2 \text{ } (m^2)}$	X	-0.22
Abdominal mass (1=no, 5=>12 cm diameter)	X	7.83
Sex (1=male, 2=female)	X	-12.3
Temperature °C	X	16.4
Stool consistency (1=well formed, 3=watery)	X	8.46
Resection (1=no,2=yes)	X	-9.17
Extraintestinal lesions (1=no,2=yes)	X	10.7
Constant		-209

The level of serum albumin contributes greatly to this index based on the authors' belief that "protein loss via the intestinal wall is the most reliable parameter to measure the inflammatory activity in the intestine". However, serum albumin is also affected by nutrition and reflects the product of both inflammatory activity and the duration of active disease (134). Advantages of this index are the avoidance of subjectivity and the incorporation of interdependent and self-correcting coefficient values. For example, there is a negative coefficient for resection to correct for soft stools due to resection and not to active disease, and coefficient of the sex variable is negative to compensate for a lower Quetelet index in females.

At a workshop on inflammatory bowel disease in Winnipeg in the fall of 1982, Dr. F.T. de Dombal related the results of a comparison among the indices and with a clinical impression of disease severity. It was found that there was a good correlation between Harvey and Bradshaw's modified CDAI and the IOIBD (Oxford) indices.

However, there was no correlation between the Dutch Index and the CDAI or the IOIBD indices. The emphasis of the Dutch Index on serum albumin may explain the poor correlation with other indices (134). There was also a moderately good correlation between clinical opinion and the CDAI and IOIBD indices, but, again, a poor correlation was noted with the Dutch Index. However, none of the indices bore a relation to the perceived need for surgery, and none of the indices gave any indication as to whether or not a patient would respond to medical therapy. The IOIBD index may be preferred on the grounds that it is fairly simple to calculate with good correlations with other indices. The participants at the workshop suggested that the IOIBD index be used in conjunction with a clinical opinion score of 0 to 4.

Hodgson (134) illustrates that there is no ideal clinical index for CD activity. Symptoms do not necessarily parallel disease activity. Many complications of CD will elevate the CDAI and other clinical scores, yet do not reflect active inflammation. For example, diarrhea usually follows resection and may be associated with lactase deficiency, bile salt wastage or bacterial overgrowth. Laboratory measures of inflammatory activity often diverge from the clinical assessments, and most are not sufficiently specific, sensitive or rapid in response to consistently correlate with clinical indices. Some acute phase reactants such as orosomucoid and C-reactive protein (CRP) correlate significantly with the CDAI (9), and with disease activity (63). The CRP level in particular is a sensitive and rapid, though unspecific, correlate of bowel inflammation (134).

METHODOLOGY

I. Selection of Patients

One hundred and thirty-seven (137) out-patients with Crohn's disease volunteered for this study. The diagnosis of Crohn's disease was made using standard radiologic, histologic and endoscopic procedures (253). Prospective subjects were contacted by telephone and volunteers were selected on the basis of their willingness and compliance. Exclusion criteria included pregnancy, the use of home TPN, residence at an excessive distance from the University of Alberta Hospital (making follow-up visits difficult), age under 18 and over 70 years, and uncertainty of diagnosis. Previous surgery, and the taking of prescribed medications or nutrient supplements were not reasons for excluding patients from the study. No attempt was made to exclude patients based on their disease activity at the time of entry, but inpatients with CD were not asked to participate in the study.

II. Patient entry

Entry and follow-up visits were conducted by three interviewers (all dietitians) on an out-patient basis in examining suites in the Clinical Sciences Building at the University of Alberta. At entry, it was confirmed that the patient understood the purpose and course of the study, and a consent form was signed. A sealed envelope was opened. This contained a single letter indicating whether the patient was randomized to the counselling or the no-counselling group. The entry questionnaire (Appendix 1) was then completed. This included a personal and medical history, information on food habits, anthropometric measurements and an assessment of the Crohn's disease activity. The patients' smoking habits were determined. Pack years was calculated by the number of cigarette packs smoked per day multiplied by the number of years the patient has smoked; previous pack years were calculated for those patients who smoked in the past but were currently non-smokers. A 48-hour nutrient intake was recorded and blood, urine and stool samples were collected. Some aspects of the medical history required later verification from the physician and/or hospital file.

III. Course of study

In Appendix 2 is shown the conduct of the 12-month study. Standard medical management was maintained throughout the study by the attending physician. The attending physician did not know whether the patient was in the counselling or the no-counselling group. Patients in the counselling group were seen for diet counselling at monthly intervals for 12 months. The study protocol of monthly counselling sessions could not always be adhered to due to patient sickness or holidays. It was found that the nutrient intake and status of a small number of patients could not be improved upon and these patients were generally only seen for counselling once between each follow-up visit. All patients, regardless of group designation, were seen for follow-up visits at the 3-, 6-, 9-, and 12-month assessment periods. Follow-up questions (Appendix 3) monitored changes in medications, nutrient supplements and eating habits. Hospital admissions, surgery and days missed from work due to Crohn's disease were noted, and the same anthropometric, clinical, nutritional and laboratory parameters as at entry were recorded.

At the 6-month visit, patients underwent a second randomization which involved taking the nutrient supplement Ensure®. The original designation of patients into the counselling or no-counselling groups remained unchanged. This second randomization provided four study groups for analysis at the 9- and 12- month assessment periods: 1) counselling plus Ensure®; 2) counselling only, no Ensure®; 3) no counselling, Ensure® only; and 4) no counselling and no Ensure®. Assessment of compliance to Ensure® and side-effects was made at the 9- and 12-month visits.

Ensure® was chosen for the study because it is nutritionally complete, ready-to-use, lactose-free, low in residue and osmolality and provides a choice of flavours. The Ensure® used in this study was donated by Ross Laboratories. The composition of Ensure® is provided in Appendix 4. The prescribed number of cans per day for the male subjects was three, for the females two, to be consumed for the entire final six months of the study. The number of cans was chosen arbitrarily to provide a measurable nutrient supplement with as little interference as possible with the normal food intake.

IV. Collection of Data

1. Clinical Assessment

At each visit, selected clinical information was recorded. These data were used to calculate the Crohn's Disease Activity Index (26)(Appendix 1, pp. 5 and 6), a modified Crohn's Disease Activity Index (122)(Appendix 5) and the Oxford Index (70)(Appendix 5). Some patients kept a record of the previous week but most relied on memory to complete the questions related to the amount of diarrhea, pain, sense of well-being and complications experienced. The interviewers reviewed the physician's files to validate information on recent complications and the presence of an abdominal mass.

2. Anthropometric Assessment

The anthropometric parameters assessed for this study are outlined on page 3 of Appendix 1, and include height (taken only at entry), weight, mid-arm circumference (AC), triceps skin-fold thickness (TSF) and mid-arm muscle circumference (MC). Height was measured without shoes. A beam balance assessed weight without shoes or heavy outer clothing. Arm measurements were conducted on the non-dominant arm using standard procedures (33). TSF was recorded as the average of three measurements using a Lange skin-fold caliper. MC was calculated from the AC and TSF measurements as described by Jelliffe (142).

Upper arm area (A), upper arm muscle area (M), and upper arm fat area (F) were derived from measures of upper arm circumference (C) converted to mm (c) and triceps skinfold (T)(96).

(1) A was calculated by the computation:

$$A(mm^2) = \frac{\pi}{4} \times d^2, \text{ where } d = \frac{c}{\pi}$$

(2) M was calculated by computation as follows:

$$M(mm^2) = \frac{(c - \pi T)^2}{4\pi}$$

(3) $F(mm^2)$ was derived as follows:

$$F(mm^2) = A - M$$

The standard for weight was that developed by the Metropolitan Life Insurance Company, 1959; the most recent 1983 tables were not available for use in this study. Standard weights in the 1959 tables are less than those in the current tables. The standard for the arm measurments was taken from the HANES I data; the 50th percentile was used as the ideal. Canadian anthropometric standards were released after the study was completed. The HANES standards are consistently higher than those in the Canadian tables.

3. Nutrient Intake Evaluation and Dietary Counselling

The method used to assess dietary intake was based on that used in the Nutrition Canada Survey (209), utilizing standardized food models. Dietary data were collected for the preceding 48 hours by the three interviewers who were all trained and experienced in this technique of dietary interview. All patients were aware that their intake would be recorded. Most patients kept a record though some relied on memory. Each food was subsequently coded by the interviewer using code numbers from Composition of Foods, Agricultural Handbook No. 8 (275), and additional code numbers created by Nutrition Canada and D.A. Smith (243). Further information on the dietary fiber, cholesterol, starch and sugar content of foods was calculated by one of the interviewers using McCance and Widdowson's text entitled The Composition of Foods (214). The total daily nutrient intake was calculated by computer and reported as the average of the two days. The nutrients which were assessed are listed in Appendix I, page 7. The nutrient intake was recorded on all patients at each visit.

The aim of the dietary counselling was to normalize the patient's nutrient status. To achieve this goal, counselling was highly individualized and dealt with the following parameters:

1. The patient's food intake and nutrient calculations were compared with Canada's Food Guide and the 1980 Recommended Dietary Allowance (RDA)(219), respectively. The goal was to at least meet the RDA for all nutrients. The recommended intake of a nutrient was raised for a patient if blood levels of that nutrient remained sub-optimal despite an intake consistently meeting the RDA (indicative of higher requirements due to disease). Nutrient allowances were also adjusted based on prescribed medications with known nutrient interactions such as Prednisone and Salazopyrin®. For example, patients taking Prednisone were usually advised to attain a calcium intake of 1000 mg per day by increasing their consumption of dairy products, and to consume a generous amount of protein (e.g. 1.5 g protein per kg ideal body weight). These allowances were arbitrarily made, as the literature provides only the rationale for increased requirements, with no estimate of the degree of adjustment to be made. Personal food likes, dislikes and intolerances were also taken into account when suggesting improvements. The dietitians did not prescribe vitamin or mineral supplements directly to the patient, but rather indicated such a need to the attending physician who then used his/her discretion. Nutrient intakes were calculated, both including and excluding any vitamin/mineral supplement. The aim was to maximize the nutrient intake from food alone. In patients with a high CDAI (e.g. greater than 300) nutrient supplements were suggested when food

intake was decreased for prolonged periods of time or when blood levels of nutrients remained low despite an intake meeting the RDA.

2. The percent ideal anthropometric values were calculated using the 50th percentile of the HANES I data as a standard. Calorie and protein allowances were adjusted based on these values. A multiple (1.75) of the basal energy expenditure was suggested some time after the study began as providing adequate calories for anabolism in patients with active inflammatory bowel disease (17). However, for purposes of this study, an additional 500 kcal above the normal daily energy intake was recommended to achieve a weight gain of one half kilogram per week, recognizing that patient response to this repletion level would vary according to disease activity. Repletion of protein stores was attempted using the formula of 1.5 g protein per kg ideal body weight.

3. The composition of the diet was modified in the presence of certain clinical symptoms of disease. Lowering of the fat intake was attempted in the presence of diarrhea, particularly that associated with steatorrhea. If the patient was bothered by bloating and gas, the possibility of a lactose intolerance was investigated by a trial of eliminating dairy products. The intake of fiber and certain foods (e.g. corn, nuts) was lowered if abdominal pain/mass or radiologic examination indicated a possible narrowing of the bowel.

4. As a measure of patient compliance and of the appropriateness of the dietary recommendations, the patient's laboratory values were examined and regarded as the most direct evidence of changing nutritional status.

No one specific diet, such as high- or low-fiber, low-refined sugar or high-protein diet, was deemed appropriate for all patients. With the exceptions noted above, the distribution of total calories consumed was set at 10-20% from protein, 30-40% from fat and 40-60% from carbohydrate. Ideal sugar and dietary fiber intakes were set at roughly 100 g and 15-20 g, respectively, to match those of typical intakes reported in the literature.

Diet sheets were not used. Some patients requested written instructions with menu ideas but the majority of the advice was verbal. The average length of time spent with the patient at each visit was one hour, of which approximately 20 minutes was devoted to diet counselling. The remainder of the hour was spent by answering the questionnaire and recording the patient's food intake of the previous 48 hours.

4. Laboratory Tests

Laboratory determinations were performed for each patient at entry and at each 3-month follow-up visit (3,6,9 and 12 months). These blood, urine and stool tests are listed in Appendix 1, pages 8 and 9. Some of the more expensive, time-consuming blood tests, such as leukocyte ascorbate, red cell folate and serum zinc and copper, were not performed at the 3- and 9-month visits if these tests had previously been normal and if the patient's health had not deteriorated. Patients usually agreed to complete urine and stool collections only at entry. All determinations were made within the Department of Laboratory Medicine, University of Alberta Hospital.

The reference ranges and standard methods used for analysis are cited in Appendix 6.

The attending physician was sent the laboratory results after a 3-month holding period. This delay was to allow any beneficial effects of diet counselling to develop. On the advise of laboratory and medical advisors for the study, exceptions in this lag time were made if potentially seriously abnormal results were noted and which were not deemed amenable to diet therapy. In these cases, the attending physician was contacted immediately and took whatever steps he/she deemed to be appropriate.

V. Statistical Methods

The collected data were keypunched and transferred to computer tape for analysis. Descriptive statistics were calculated for each variable. Chi-square analysis and cross tabulations were used to investigate the relationships among qualitative (discreet) variables. Relationships among quantitative or continuous variables were determined by analysis of variance (ANOVA). Pearson correlation coefficients (77) were calculated among the selected nutrient intakes, anthropometric measurements, laboratory data and the CDAI. A principal factors analysis (285) was performed on these variables to estimate the principal axes of variation (Table 29). Paired t-tests estimated significance of change in CDAI between time periods.

A square root transformation was applied to the CDAI variable due to skewness of the data (Table 27). Spearman correlation coefficients were calculated among the three indices of disease activity due to the non-parametric scale of these data (Figure 4). Change in the Oxford and modified CDAI was assessed by the Wilcoxon matched-pairs signed-ranks test (Table 44).

To test the null hypothesis that there was no effect by counselling on the CDAI and other nutrient intake, anthropometric or laboratory parameters, analysis of covariance (ANCOVA) was applied (for example, Table 41). The literature suggested the inclusion of age, duration of disease and season of study entry as covariates. Main effects variables were counselling, sex and prior history of small bowel surgery. ANCOVA was also used to test the null hypothesis that Ensure® supplementation had no effect on CDAI or medications. The same parameters were selected as covariates and main effects, with the addition of dose of medication as a covariate and Ensure® compliance as a main effect. Newman-Keul Multiple Range Tests evaluated the significance between time periods of differences among the means (for example, Table 42). The Irwin-Fisher Exact Test (188) was used to determine the difference between proportions (for example, Table 14).

RESULTS

I. Patient Characteristics at Entry

1. Demographics

One hundred thirty seven (137) outpatients with known Crohn's disease (CD) were entered into this study. Twenty-one patients dropped out of the study before completion (Table 1), 14 (21%) from the counselling group (C) and 7 (10%) from the no-counselling group (NC). Nine (43%) drop-outs occurred in the first three months, three (14%) between the three and six month assessment, four (19%) between the six and nine month visits and five (24%) in the nine to twelve month period. Reasons for dropping out were as follows: twelve moved to another city or province, two became pregnant, one died, two found it too difficult to attend the monthly diet counselling sessions (one was elderly and dropped out during the winter, the second was hampered by a prolonged bus strike), two were placed on TPN (a criteria for exclusion) and two became unwilling to participate further in the study and dropped out shortly after entry.

The characteristics of the 21 patients not completing the study and of the 116 patients who participated for the full 12 months are shown in Table 2. There were no significant differences in the characteristics of those patients completing and not completing the study.

Tables 3 and 4 provide information on the males and females at study entry, and on the C and NC groups into which all patients were randomized. The duration of disease was significantly longer for females than for males, 7.4±5.0 versus 5.6±4.0 years, respectively.

Patients in C were significantly older than NC, 35.5±12.0 versus 31.5±17.5 years, respectively. At study entry, the Crohn's Disease Activity Index (CDAI) was significantly higher in C than in NC, 132±106 versus 92±84, respectively. The mean CDAI was greater in females than in males, 124±103 versus 96±89, but this difference was not statistically significant. Subsequent analyses were adjusted for differences in age and disease activity between the two study groups. The amount of bowel resected, percent ideal body weight and smoking habits were similar in males and females, and in C and NC.

The site of intestinal involvement with CD and the patient's intestinal tract surgical history was similar in males and females, and in C and NC (Table 4). Thirty-three percent of patients had small bowel disease only, 60% had involvement in both small and large bowel, and the remainder (7%) had CD restricted to the large bowel. Forty five percent (61/137) of the patients in the study had never had CD-related surgery. A smaller number of the females and of C had previously undergone gallbladder surgery ($p<0.05$). A greater number of females had metabolic bone disease, although this difference was not statistically significant. An ileostomy/colostomy was present in 5% of males and in 6% of females. Renal calculi were a complication in 9% of males and in 6% of females. Ankylosing spondylitis was noted in 12% of males but in none of the females. Twenty-two percent (30/137) of the patients stated they were intolerant to milk, and 50% (68/137) were taking vitamin and/or mineral supplements.

Fifty percent of the patients entered in the study were diagnosed after 1975 (Figure 1). The distribution of patients by month of diagnosis of CD is shown in Figure 2. The greatest proportion of patients were diagnosed in January and in April, 12% and 13% respectively. The percent of patients diagnosed during the winter (December through February) and during the spring (March through May) was higher than during the other seasons (26% and 33% for winter and spring versus 20% and 21% for summer and fall). The percent of patients diagnosed in the spring was significantly higher than the proportion diagnosed in the summer or in the fall, $p<0.05$.

The medications taken by the patients at study entry are shown in Table 5. The proportion of patients taking prednisone or Salazopyrin® was 42% and 47%, respectively. There was no significant difference between C & NC in the proportion of patients taking Prednisone or Salazopyrin®. Twenty percent of patients at entry were taking both medications. Twelve percent and 15% of patients were taking Flagyl® or other antibiotics, respectively. Twenty-one percent of patients were taking an anti-diarrheal agent. Seventeen percent of female patients were taking an oral contraceptive agent.

The medications taken by site of CD are shown in Table 6. Somewhat surprisingly, 40% of patients with large bowel disease only were taking Prednisone, and 40% of patients with small bowel disease only were taking Salazopyrin®. The National Cooperative Crohn's Disease Study did not find these medications to be useful at these disease sites. There were no significant differences in the proportion of patients taking any medication by site of disease.

The anthropometric data of males and females, and of C and NC at study entry are shown in Table 7. The means of the various measurements were close to, or exceeded, the ideal. Muscle indices were consistently the lowest, with means ranging from 84% to 93% of the ideal. Triceps skin-fold and fat area correlated highly ($p<0.01$). Muscle circumference and muscle area were also highly correlated ($p<0.01$). The percent ideal mid-arm circumference was significantly higher in the females than males ($p<0.05$). The anthropometric data were otherwise similar in males and females.

The possible edematous and muscle-wasting effects of Prednisone medication on these arm measurements were investigated. However, for none of the anthropometric measurements was there a significant difference in the mean percent ideal between those patients taking and those not taking Prednisone at the time of study entry (Table 8).

2. Nutrient Intake at Entry

Nutrient intakes are reported as the mean of two-day dietary records/recalls and exclude any contribution by nutrient supplements. The nutrient intakes of patients at study entry (Table 9) demonstrate the expected differences in the quantity of intake between the sexes, with values higher in males than females. The mean intakes of these patients with CD were generally lower than those from the Nutrition Canada survey (1973), except for vitamin C and total folate in both sexes and crude fiber in the females. However, mean intakes in the current study exceeded current dietary standards, except for calcium, iron and folate in females and folate in males.

Because of the wide range of variation in the nutrient intake data, the proportions of patients who consumed the full and partial recommended daily allowance (RDA) for these nutrients was examined. This information for males and females at entry is shown in Tables 10 and 11, respectively. Significant differences ($p<0.05$) in these proportions between the sexes were found for energy, protein, calcium, phosphorous, iron, thiamin, riboflavin, vitamin B_{12} and folate, with males consuming the higher intake. The difference in vitamin C intake between males and females was almost significant ($p=0.052$).

Since the caloric intake of males was greater than females, the nutrient density (nutrient intake per 1000 kcal) was calculated for the two sexes (Table 12). The nutrient density was greater in females for calcium, phosphorous, vitamin A and carotene; the density for preformed vitamin A, niacin and cholesterol was greater in males. However, none of these differences were significant. Thus, the poorer quality of the intake of females vs males (Tables 10 and 11) is due to a lower energy intake and not to a lower nutrient density of that intake.

In Table 13 is presented the mean nutrient intakes of C and NC at study entry. The intake of vitamin or mineral supplements was not included in these means. The mean intake of these patients exceeded current recommended daily allowances for all nutrients except folate. There were no significant differences in intake means between C and NC.

Intake data for C and NC were categorized according to full and partial RDA standards as was previously done for males and females. The proportion of patients who achieved their full and partial RDA is given for study entry in Table 14. The proportion of patients consuming the full RDA for protein was greater in NC than in C ($p<0.05$). No other differences in intake were significant.

High positive correlation coefficients were observed between a number of selected nutrient intakes (Table 15), in particular protein and niacin, iron and niacin, calcium and riboflavin, and calcium and phosphorous, crude fiber and dietary fiber. These correlations were significant at p<0.01.

3. Hematological and Biochemical Assessment at Entry

The mean, standard deviation and range of hematological values of patients at study entry are given in Table 16. All means fell into the normal reference range. A high proportion of patients had abnormal laboratory values for serum iron (52% of males, M and 39% of females, F), serum ferritin (M24%, F20%) transferrin saturation (M52%,F61%), total iron binding capacity (M14%,F23%), total lymphocytes (M48%,F47%), red cell count (M8%,F28%) and mean red cell volume (M25%,F25%). No patients had a low white blood cell count or an elevated prothrombin time at study entry. There was a significant difference in the proportion of males vs females with a high and low value for serum ferritin, a high total iron bindng capacity and a high mean red cell volume (p<0.05) and a low red blood cell count (p<0.01).

The mean, standard deviation and range of biochemical values of patients at study entry are shown in Table 17. A high proportion of patients had an abnormal creatinine height index (M32%,F38%) alkaline phosphatase (M21%,F17%) serum carotene (M16%,F24%) serum vitamin C (M11%,F18%) and white cell vitamin C (M26%,F49%). Significantly more females had a low white cell vitamin C level (p<0.01). No patients had a low serum albumin, serum calcium or serum vitamin A at study entry.

In Table 18 is presented the mean laboratory values of the C and NC at study entry. There were no significant differences noted between the means of the laboratory values in the two study groups.

The proportions of patients in C and NC who had abnormal hematological and biochemical values at study entry are shown in Tables 19 and 20, respectively. There were no significant differences between C & NC in the proportion of patients with abnormal values.

Some controversy surrounds the accepted lower limit of normal for several of the hematological and biochemical parameters. Table 21 shows a number of accepted reference ranges for hemoglobin, serum albumin, serum folate, serum vitamin C and white cell vitamin C. Those patients with laboratory values lower than the reference figure are at risk of developing a deficiency of that nutrient. This table illustrates how the reference selected can affect interpretation of the health status of this population. For example, depending on the lower limit of the reference range that is selected for serum folate, the proportion of this population defined as at risk of deficiency ranges from 10 to 62%. It must be emphasized, however, that comparison of reference ranges from one laboratory to another is not valid if the methodology of the laboratory test differs.

Correlation coefficients among hematological and biochemical data are shown in Table 22. Only serum folate and red cell folate levels correlated significantly. It is of interest to point out that there was no correlation between serum vitamin C and white cell vitamin C, or between serum iron and ferritin.

4. Urinary and Fecal Collection Data at Entry

At study entry 24-hour urine and 48-hour stool collections were made by 60 and 56 Crohn's patients, respectively. These data are presented in Tables 23 and 24. Note the wide range of values obtained in these measurements. A high proportion of patients demonstrated elevated levels of urinary creatinine (M32%,F20%) phosphorous (M48%,F31%), and calcium (M36%,F17%) (Table 23). Fecal fat, bile acids and weight were elevated in 41% (M40%,F42%), 75% (M72%,F77%), and 58% (M68%,F48%) of patients, respectively (Table 24). There were no significant differences between males and females in the proportion of patients with abnormal urinary or fecal values. The mean fecal fat, bile acids and weight by site of Crohn's disease are in Table 25. There were no significant differences between the groups, although this may be due, in part, to the large standard deviations for each parameter, and the small number of patients with CD of the large bowel only who submitted fecal collections.

There were a number of significant correlations among selected fecal, urinary, blood and clinical values (Table 26): fecal weight and fecal fat, fecal weight and fecal bile acids, fecal bile acids and fecal fat, fecal fat and urinary oxalate, fecal bile acids and urinary oxalate, fecal fat and serum carotene (inverse relationship), the coefficient of fat absorption and Crohn's Disease Activity Index (inverse relationship), and, finally, urinary phosphorous and serum phosphorous (inverse relationship).

II. Indices of Crohn's Disease Activity

The CDAI has been presented in the original scale in Tables 2 and 3. However, this index was found to be skewed due to the relative good health of our patient sample. This skewness is illustrated in Figure 3 where the majority of patients at entry had inactive disease

(CDAI equal to or less than 150). To facilitate further statistical analysis, the CDAI was transformed to reduce this skewness. Table 27 illustrates the mean, variation, range and skewness of the original CDAI plus two transformations, the log and the square root. It was found that the square root transformation √CDAI brought the skewness closest to zero.

In addition to the CDAI, the Harvey and Bradshaw modified CDAI and the Oxford index were also calculated in this study. Figure 4 illustrates the high Spearman correlation coefficients among the transformed √CDAI, the Harvey and Bradshaw modified CDAI, the Oxford index. The transformed CDAI was rounded for this analysis to match the ordinal scale of the other indices.

Due to the low amount of skewness and the high correlation with other indices of activity, the square root transformation of the CDAI (√CDAI) will be cited in all subsequent tables. A further advantage of the √CDAI is that, as a continuous variable, it is superior to the ordinal scale as a dependent variable in analysis of covariance, and is more sensitive to variance distribution.

III. Correlations Among Selected Nutrient Intake, Laboratory and Clinical Parameters

Significant positive correlations were noted between serum vitamin A and vitamin A intake, serum vitamin C and vitamin C intake, hemoglobin and iron intake, and hematocrit and iron intake (Table 28). Only data from those patients not taking a nutrient supplement were utilized in these comparisons. A further assessment that was performed was the change in laboratory value from entry to six months plotted against the change in intake within each individual. The measurements assessed were iron intake vs serum iron and serum ferritin, vitamin A intake vs serum vitamin A and serum carotene, vitamin C intake vs. serum vitamin C and white cell vitamin C, vitamin B_{12} intake vs. serum vitamin B_{12}, and folate intake vs. serum folate and red cell folate. Of these, only the correlation of change in iron intake vs. change in serum iron was signifcant ($p<0.01$). This information is not provided in a table.

Intakes of energy, dietary fiber and fat, but not sugar, correlated highly with the Crohn's Disease Activity Index (Table 28). The transformed Index ($\sqrt{\text{CDAI}}$) correlated signficantly with the following laboratory parameters: hemoglobin, hematocrit, serum iron, transferrin saturation, red blood cell count, mean red cell volume, serum albumin, serum protein, serum zinc and red blood cell folate. Again, only data from patients not supplementing their intake with the nutrient in question were used in these analyses.

Since a number of intake, laboratory and clinical parameters were found to be correlated, the communial variation within these correlations was summarized by a principal components analysis (Winer, 1971). The principal axis of variation in this study was intuitively defined as being the general health or well-being of the patient. In Table 29 factor 1 lists those variables that ranked the most highly with overall health. In descending importance, factors 2 to 7 are also listed. Except for the $\sqrt{\text{CDAI}}$, only those variables with correlations equal to or greater than .60 are cited. This table shows that numerous variables are necessary to estimate patient well-being. The $\sqrt{\text{CDAI}}$ had a low correlation coefficient, and thus was shown to be independent of nutrient intake, anthropometric and laboratory variables as an estimate of patient well-being.

IV. Effects of Diet Counselling on Nutrient Intake and on Anthropometric, Laboratory and Clinical Variables

1. Nutrient Intake

The proportions of C and NC taking vitamin and mineral supplements are outlined in Table 30. The proportion of patients in each study group who received supplements did not change significantly over time. Therefore, in examining the effect of counselling on nutrient intake, only the nutrient intake from food will be reported.

Table 31 shows the mean nutrient intake of C and NC at study entry and at three months and six months. The mean intakes of all nutrients, except folate, met the current recommended dietary allowances at all time periods. As just explained, the intake of vitamin or mineral supplements was not included in these means. As previously noted, there were no significant differences in mean intakes between C and NC at entry. At three months C had significantly higher mean intakes of vitamin C ($p<0.01$) and folate ($p<0.05$) compared to NC. At six months, C had significantly higher intakes of vitamins A and C, and crude fiber ($p<0.01$) compared to NC. Within C over time there were increases in the mean consumption of protein, crude fiber, calcium, phosphorus and vitamin A, while that of vitamin B_{12} decreased from entry to six months. However, only the change in mean crude fiber intake was statistically different ($p<0.01$) in C vs. NC.

In Table 32 is shown the wide range of intakes for each nutrient. The ranges are particularly wide for calcium, phosphorus and vitamins A, C and B_{12}. Such wide ranges result in the large standard deviations shown in Table 31.

Analysis of covariance was done on energy and protein intake to assess changes in mean intake due to counselling. These nutrients had been selected from the principal factor analysis as representative intake parameters to assess patient well-being (Table 29). These analyses are not shown in a table, but their findings will be described. Covariates were initial intake, age, season of entry, duration of disease, and entry $\sqrt{}$CDAI. Counselling and sex were the main effects studied.

In the analysis on energy intake, initial energy intake was the only covariate to account for a significant amount of variation. Of the main effects, counselling did not significantly affect energy intake, but patient sex did. Covariate analysis adjusts the means by removing the variation contributed by each of the covariates. Adjusted mean intakes of energy were similar in C and NC. However, as expected, females consumed significantly less energy than did males.

The findings for protein intake were similar to those of energy intake. Initial protein intake was the only covariate to account for a significant amount of variation. Counselling did not affect protein intake significantly, but the sex of the patient did affect intake. While the adjusted mean protein intake of C was higher than that of NC, this was not significant. Females consumed significantly less protein than did males.

The normal mean nutrient intakes seen in Table 31 masked a subgroup of patients consuming inadequate amounts of each nutrient. Intakes were classified into a number of subdivisions of the Recommended Daily Allowances (RDA), designated as 1/3, 1/2, 2/3, or full RDA. These intakes are those from food alone, excluding any contribution from nutrient supplements. In Table 33 is shown the substantial proportions of patients in each of C and NC who consumed less than the full RDA. Protein, phosphorus and niacin intakes were the most generous. That is, the majority of patients consumed the full RDA for these nutrients at all assessment periods. Calcium, iron, vitamin A, vitamin B_{12} and folate were the most poorly consumed at all assessment periods. At six months compared to entry, counselling was associated with significant increases in the proportion of patients consuming the full RDA for protein, riboflavin and vitamin C ($p<0.05$). No significant changes in the consumption of the full RDA were noted in NC. Table 34 illustrates the magnitude of change in the proportion of patients from each of the C and NC groups who consumed either the full RDA or at least 2/3 RDA. For example, in C from study entry to six months (0-6), there was an increase of 20% (+20) in the number of patients consuming at least 2/3 RDA for energy. This table shows that by six months, the proportion of C consuming the full RDA increased by at least 10% for energy, protein, calcium, phosphorous, vitamin A, riboflavin and vitamin C. As noted in Table 33, this increase was significant for protein, riboflavin and vitamin C ($p<0.05$). Energy, calcium, vitamin A, riboflavin and vitamin C showed increases of at least 20% in the proportion of patients categorized into the >2/3 RDA subdivision. In NC, only calcium and riboflavin intakes showed consistent improvement in the six month period. It should be noted that improvements could not be expected in the intake of niacin since all patients consumed close to the full RDA at entry.

Iron and folate intakes of C showed no change or even a decline in quantity consumed over time. However, the RDA for these two nutrients has long been criticized as being unjustifiably high and unattainable in a normal diet, especially for women. The most recent (1983) Canadian Recommended Nutrient Intakes (RNI) suggest a daily iron intake of 8 mg for adult males and 14 mg for adult females, compared to the 1980 RDA of 10 mg and 18 mg, respectively. The 1983 RNI for total folate is 220 μg for adult males and 175 μ for adult females compared with the 1980 RDA of 400 μg. Counselling was associated with a greater number of patients consuming at least $^1/_2$ RDA for iron (75% at entry vs. 85% at six months) and a significant increase ($p<0.01$) in the proportion of patients consuming at least 1/3 RDA for folate (61% at entry vs. 83% at six months). However, intakes of these two nutrients would have remained suboptimal even if using the new lower standards.

2. Anthropometric Measurements

Percent ideal body weight was selected from the principal factors analysis (Table 29) as a representative anthropometric parameter to assess well-being. Analysis of covariance was performed on percent ideal body weight. The results will be described but are not shown in a table. Of the covariates that were studied, initial % ideal weight and duration of disease were found to account for a significant amount of variation. Covariate analysis found no significant effect of counselling, sex, or history of small bowel surgery on the mean percent ideal weight. Interactions were found between counselling and sex ($p<0.05$) and between sex and small bowel surgery ($p<0.10$). Adjusted mean percent ideal weights remained greater than 100% at all time periods. Mean percent ideal weights were similar within all the main effect categories.

Table 35 outlines the unadjusted changes over time in mean percent ideal body weight, mid-arm circumference (MAC), triceps skinfold (TSF) and mid-arm muscle circumference (MC) within C and NC. The ideal was taken as the 50th percentile of the appropriate sex and age from the HANES I data (113) for the arm measurements; the standard for weight was that developed by the Metropolitan Life Insurance Company in 1959, (198). The means, as percent of ideal, changed little over time in either group except for the mean value of the TSF which decreased numerically in both groups. This decrease was not significant. Weight and TSF means remained above ideal levels for the entire study; MAC means remained just less than 100% ideal and MC ranged from the low- to mid-90% ideal level.

The 5th percentile has been suggested as the criteria of depletion (107). To adapt the study numbers as coded to this criteria, it was found that 85% of ideal for MAC and MC, and 45% of ideal for TSF approximated this criteria of depletion. Table 35 shows that the proportion of patients in C who were classified as depleted exhibited a tendency to decrease over the first six months of the study. The uncounselled group did not show such a trend. The most pronounced improvement in C was the MC measurement. At entry, 20% of

C were depleted (i.e. MC less than 85% of ideal). By six months, this figure had dropped to only 9% of the group showing evidence of depletion. However, this decrease was not statistically significant.

3. Laboratory Tests

Table 36 shows the mean laboratory values in C and NC at entry, three months and six months. All means remained above reference values at all time periods in both study groups. There were no significant differences between the means of C and NC at any time.

Hemoglobin, transferrin saturation and serum albumin were selected from the principal factors analysis (Table 29) as representative laboratory parameters to assess well-being. Covariate analysis was again used to study the effects of counselling on these laboratory parameters. Variables chosen as covariates were initial laboratory value, age, season of entry and duration of disease. Main effects categories were counselling, sex and small bowel surgery. Covariate analysis demonstrated no significant effect of counselling or sex on the mean laboratory values. However, for each laboratory parameter, previous history of small bowel surgery resulted in significantly lower mean laboratory values ($p<0.05$). Interactions occurred between counselling and sex ($p<0.10$) to influence hemoglobin, between counselling and surgery ($p<0.05$) to affect transferrin saturation, and between sex and surgery ($p<0.10$) to affect serum albumin. These normal means masked a subgroup of patients with low laboratory values.

The proportion of patients whose lab values fell outside the reference range is given for entry, three months and six months for C and NC (Tables 37 and 38). The proportion of patients in C who had a low hematocrit and serum ferritin value increased significantly ($p<0.05$ and $p<0.01$, respectively) from entry to 6 months. The proportion of patients in NC who had a low serum ferritin and serum magnesium value increased significantly ($p<0.01$ and $p<0.05$, respectively) from entry to 6 months. The proportion of NC who had a low red blood cell count at entry decreased significantly by 6 months ($p<0.05$). Changes in these proportions over time are illustrated in Table 39. For example, from entry to six months (0-6), C showed a decrease of 14% in the number of patients with a low total lymphocyte count. The proportion of counselled patients with a low hemoglobin, hematocrit, serum iron or serum ferritin concentration increased at least 10% in the first six month period. Those counselled patients with a low total lymphocyte count, serum vitamin C and white cell vitamin C decreased by 14%, 10% and 13%, respectively, in the first six months. Changes in the other laboratory parameters were less than 10%.

In a further attempt to identify any effects of counselling on laboratory data, the proportions of patients changing from low to normal and from normal to low lab values were calculated on selected measurements (Table 40). Counselled patients normalized their serum vitamin C level significantly more frequently than uncounselled patients from entry to three months ($p<0.01$) and from entry to six months ($p<0.05$). As well, significantly more C than NC normalized their total iron binding capacity, serum folate and white cell ascorbate levels from entry to six months. Fewer patients in C than NC dropped to a sub-optimal level of red cell folate and white cell ascorbate from entry to three months ($p<0.01$ and $p<0.05$, respectively) and from entry to six months ($p<0.01$). Fewer counselled patients dropped to a low level of total iron binding capacity from entry to six months ($p<0.01$). However, more NC than C normalized their serum ferritin, serum folate, red blood cell folate and white cell ascorbate levels from entry to three months ($p<0.01$), and their red cell folate level from entry to six months ($p<0.01$). It is difficult to draw any definite conclusions about the benefits of counselling from this table.

4. Crohn's Disease Activity Index

The counselling group (C) began the study with a significantly higher mean activity index and age ($p<0.05$) (Table 3). In order to diminish differences at entry between C and NC, covariate analysis was used to assess the effect of counselling on disease activity. In addition to the initial $\sqrt{CDAI}$ the season of study entry, patient age and duration of disease were intuitively chosen as further covariates. The main effects were counselling and sex. Previous history of small bowel surgery was chosen as the final main effect, with deference to the possibility of diminished response to nutritional therapy with reduced functional bowel area.

Of the covariates that were chosen, only the initial $\sqrt{CDAI}$ value accounted for a significant amount of variaton in subsequent $\sqrt{CDAI}$ values. Table 41 illustrates that counselling had a significant effect ($p<0.05$) on the $\sqrt{CDAI}$ in the first 3 months of study, and that this effect was maintained for the next 3 months. Sex of the patient and history of small bowel surgery each had independent but smaller effects on the $\sqrt{CDAI}$ ($p<0.10$). In the first 3 month period, counselling and bowel surgery interacted significantly ($p<0.05$) to affect the $\sqrt{CDAI}$.

The nature of the main effects on the $\sqrt{CDAI}$ is illustrated in Table 42. This table presents the mean disease activity values after the effects of the covariates have been removed. The adjusted means are presented in the transformed square root scale ($\sqrt{CDAI}$) as well as in the original scale (i.e. $\sqrt{CDAI^2}$). Counselling was associated with a significant decline in CDAI in the first 3 months relative to the no counselling group, a decline which was maintained a further 3 months. Females showed a drop in CDAI relative to males in the 0 to 6 month periods, though significance was only at the 10% level. Patients with no previous history of small bowel surgery also showed a decline in CDAI from 3 to 6 months compared with those who had undergone surgery, but again only at the 10% level of significance. However, as was indicated in Table 41, the interaction between counselling and surgery was significant ($p<0.05$) so that only those patients with no small bowel surgery showed a response to counselling in the first 3 months of the study.

Figure 5 illustrates the changes in CDAI of C and NC for the first six months of the study. The adjusted $\sqrt{CDAI}$ values converted to the original scale (i.e. $\sqrt{CDAI^2}$) are presented. The decrease from 111 to 89 in C from entry to three months was significant ($p<0.05$). The CDAI of C further dropped to 77 by six months, though this change was not significant. The CDAI of NC increased over this period of time so that by six months the mean value of the group was 89, and exceeded that of C. However, changes in NC were not significant.

Figure 6 illustrates a further way of looking at the improvement in disease activity associated with dietary counselling. In this figure, the change in the number of counselled patients with moderate to severe disease is compared to that of the uncounselled group. The criteria for moderate to severe disease was defined in the original CDAI as an index score of greater than 150 but less than 450. At study entry 40% of C had moderate to severe disease compared to 19% of NC. This difference was significant ($p<0.01$). After six months, 31% and 29% of patients in C and NC, respectively, had active disease.

Finally, Table 43 compares the proportion of patients in C and NC in which the CDAI changed from active (greater than 150) to inactive (less than or equal to 150), and from inactive to active. After six months of counselling, the disease became inactive in 22% of C compared to 8% of NC. This difference between C and NC was signifcant ($p<0.05$). Conversely, the disease worsened (became active) in 12% of C compared with 18% of NC. This difference was not significant.

Covariate analysis and transformation procedures were not applied to the modified CDAI or to the Oxford index since $\sqrt{\text{CDAI}}$ was judged the best index for this study for reasons described in section II. However, the Harvey and Bradshaw modified CDAI and Oxford indices have the advantage of potentially reduced subjectivity. For this reason, the effects of counselling on these more objective assessments of disease activity were analyzed and the results are presented in Table 44. Note that the net change (i.e. decline) in each index over the first six month period was significant in C but not in NC, as assessed by the Wilcoxon test.

5. Surgery, Hospitalization and Work Lost due to Crohn's Disease

The amount of surgery, hospitalization and work lost due to Crohn's disease was assessed to evaluate the possible clinical implications of diet counselling. Table 45 illustrates that 8 and 7 patients from C and NC, respectively, required surgery in the first six months of study. There were 14 and 16 hospital admissions in C and NC, respectively, for an average length of stay of 11.1 and 13.5 days, respectively. The number of days in hospital was significantly less in C vs. NC from three to six months ($p<0.01$) and from entry to six months ($p<0.05$).

Instances of work being missed due to Crohn's Disease occurred 23 times and 30 times in C and NC, respectively, in the first six months of the study (Table 46). The number of days unable to work was significantly less in C vs. NC from three to six months from entry to six months ($p<0.01$). The mean number of work days missed per patient was 12.9 and 17.5 days for C and NC, respectively.

6. Prednisone & Salazopyrin® Therapy

The effects of diet counselling on drug therapy were assessed. Covariate analysis was again deemed appropriate in assessing changes in the need for medication. Initial dose of medication, age, season of study entry and duration of disease were intuitively chosen as covariate variables. Sex was selected in addition to counselling as a main effect. This information was not incorporated into a table.

Of the covariates, only initial dose of Prednisone accounted for a significant amount of variation ($p<0.01$). Counselling and sex affected the dose of Prednisone in the first three months of study,

$p<0.10$ and $p<0.01$, respectively. Counselling was associated with a significantly lower dose of Prednisone, 4.0 mg vs. 6.5 mg/day for C and NC, respectively, in the first three months of study. In this time period, females were taking significantly less Prednisone than were males.

Of the covariates in the Salazopyrin® analysis, the initial dose of Salazopyrin® was the only covariate to account for a significant amount of variation. Counselling and sex each significantly affected the dose of medication in the 3-6 month period, $p<0.10$ and $p<0.05$, respectively, and in the entry to 6 month periods ($p<0.05$). Counselling and sex also interacted significantly from 3 to 6 months ($p<0.10$). Counselling was associated with a significant ($p<0.05$) decrease in the amount of Salazopyrin® required from entry to the 6 month period. As with Prednisone, females had a significant ($p<0.05$) and independent lowering of their dose relative to males.

Tables 47, 48 and 49 present descriptive information on the changes in medications associated with counselling. At study entry, 48% and 36% of C and NC, respectively, were taking Prednisone (Table 47). These proportions changed to 39% and 35% at 3 months, and 37% and 39% at 6 months. These changes were not signifcant. Forty-two percent and 53% of C and NC, respectively, were taking Salazopyrin® at entry. These proportions changed to 36% and 47% at 3 months, and 32% and 50% at 6 months. Again, these differences were not significant.

The mean dose of each medication decreased over time in C. However, when looking at only those counselled patients taking either medication, the mean dose increased by 6 months. In NC the mean dose of Prednisone increased while the Salazopyrin® dose remained constant. The mean dose of each medication for only those uncounselled patients taking the medication was elevated above the entry dose at all subsequent time periods.

Table 48 illustrates that a consistently larger proportion of C was able to stop taking or decrease the daily dose of Prednisone or Salazopyrin® compared to NC. The proportion of C that was able to stop taking Salazopyrin® was significantly greater than that of NC ($p<0.05$) for the entry to six month period. In C, the size of dose decrease was greater than in NC for Prednisone during the entry to six month period, and for Salazopyrin® during both the entry to three month and entry to six month time periods. During the first six months of study, a 1.0 unit change in $\sqrt{}$CDAI was associated with a 1.66 tablet/day change in Prednisone and a 0.38 tablet/day change in Salazopyrin®.

Fewer counselling than no counselling patients had to begin taking Prednisone during the first six months of the study (Table 49). However, there were no major differences between C and NC for the proportion of patients having to begin taking Salazopyrin®. The proportion of patients having to increase their dose of either medication tended to be similar in C and NC. The size of the dose increase of Prednisone was less in C at both time periods, but greater in C for Salazopyrin® at both time periods.

V. Randomization to Ensure®

1. Characteristics of Ensure® Study Groups

At six months C and NC were comparable in all variables except for significantly higher mean intakes of crude fiber, vitamin A and vitamin C in the counselled group ($p<0.01$). At this time, patients in C and NC were further randomized into an Ensure® supplement or no Ensure® supplement group, resulting in four study groups at nine and twelve months: counselling plus Ensure® (C+E), counselling only (C), no counselling plus Ensure® (NC+E), no counselling and no Ensure® (NC). All four groups were comparable at randomization (Table 50) except for age where C was significantly older than NC ($p<0.05$).

2. Compliance To Ensure®

The prescribed number of cans of Ensure® to be taken daily was set at three for males and two for females. Three months after randomization, at the nine month visit, 33% of the 58 patients randomized either to C+E or NC+E had stopped taking Ensure® for various reasons. At this time only 28% were taking 50% or more of the prescribed number of cans per day. By twelve months, 55% of patients had stopped taking Ensure®, and only 18% were taking at least half of the prescribed amount daily. The mean number of cans consumed per day at each of the nine and twelve month assessment periods was 0.8±0.8. Compliance by males and females was similar; at nine months, 28% and 36% of males and females, respectively, had stopped taking Ensure®. By twelve months, 52% and 59% of males and females had stopped.

Close supervision had a substantial influence on patient compliance (Table 51). The percent of prescribed cans of Ensure® consumed was higher in the counselled group at nine and twelve months. The number of counselled patients stopping Ensure® was lower at twelve months, though this difference was not statistically significant.

Numerous possible side effects have been ascribed to the intake of defined formula diets. Patients were directly questioned for these possible symptoms. Table 52 describes the proportion of patients who experienced various problems with the consumption of Ensure®. The most commonly reported side effects were dislike of the flavor, bloating, reduction in appetite, diarrhea, and gas. While diarrhea, gas, bloating and pain are common symptoms of active CD, these side effects were felt by the patients to be present to an extent over and above their normal discomfort, and were thus ascribed to the consumption of Ensure®. These side effects probably contributed to the poor compliance. At each time period, the proportion of non-compliant patients reporting side effects was greater than that of the compliant groups (Table 52). By twelve months only seven patients remained taking the prescribed amount of Ensure®, and only one of these patients reported a side effect, that being diarrhea.

3. Effects of Ensure® on Nutrient Intake, and on Anthropometric, Laboratory and Clinical Variables

A. Effects of Ensure® on Nutrient Intake

The mean nutrient intakes of the patients in this study were generally within the normal range at all time periods. Therefore, to gain a better indication of the effects of Ensure® supplementation on nutrient intake, we chose again to use the full RDA criteria. Tables 53 and 54 show the change in the proportion of patients consuming the full RDA for each nutrient. The six month intake is from food alone to provide a standard for comparison. The nine and twelve month intakes combine the values from food and Ensure®.

Table 53 depicts the nutrient consumption of the four counselling-Ensure® groups: C,C+E, NC, NC+E. Comparing the six month intake from food alone to that of the nine and twelve month periods, Ensure® supplementation in the counselled group (C+E) appeared to improve the intake of vitamin B_{12}, but the proportion of patients meeting the full RDA for protein, calcium, phosphorous, vitamin A, riboflavin and vitamin C showed a substantial decrease when Ensure® was added to the diet. However, none of these changes were significant. In the uncounselled patients (NC+E), Ensure® again did not improve nutrient intake to any degree. Calcium and vitamin C intakes even worsened. The proportion of patients consuming the full RDA in the no Ensure® groups also showed fluctuations from one time period to another. Relative to these random fluctuations, assignment to the Ensure® group cannot be said to either improve or worsen the total nutrient intake.

Since compliance to Ensure® was poor, changes in the nutrient intake were assessed after dividing study patients into groups according to the degree of compliance. Randomization to C or to NC was ignored for the moment. The three groups that were compared are defined as follows: 1. No Ensure® - patients not randomized to Ensure®; 2. Ensure®, compliant - patients randomized to the Ensure® group who did not stop taking Ensure®; and 3. Ensure®, stopped - patients randomized to the Ensure® group but who stopped consuming it at some point in time. The compliant Ensure® group consisted of 38 patients at nine months and 24 patients at twelve months. At nine months, this group was consuming 48%±27% of prescribed cans (range 4-100%); the mean number of cans consumed per day was 0.8±0.8. At twelve months, this group consumed 46%±32% of prescribed cans (range 13-100%); the mean number of cans consumed per day was 0.8±0.8. From six to nine months, the Ensure®-stopped group consumed a mean of 8% of the prescribed amount of Ensure® before stopping (range 0-33%). From nine to twelve months, a mean of 6% had been consumed (range 0-42%) before the patients stopped taking their prescribed Ensure®.

Table 54 depicts the nutrient consumption according to these compliance groups. Compliance to Ensure® was associated with a decreased vitamin A intake, though this was not significant. The intake of vitamin B_{12} improved significantly with Ensure® compliance, $p<0.05$. Thiamin intake improved in the Ensure®-stopped group, but this change was not significant. Vitamin C intake worsened significantly by twelve months ($p<0.05$). The decrease in vitamin A intake from six to nine months was also significant ($p<0.05$).

In summary, the quality of the overall nutrient intake was not enhanced by taking Ensure®. The only nutrient to show a significant improvement with compliance to Ensure® was vitamin B_{12}. Furthermore, since the combined intake from food and Ensure® was similar to that from food alone, it is obvious that the intake of food declined when Ensure® was added to the diet.

B. Effects of Ensure® on Percent Ideal Body Weight

Principal factors analysis (Table 29) showed the percent ideal body weight to be a good anthropometric estimate of general well-being. Table 55 shows that changes over time in mean percent ideal weight were minimal, regardless of Ensure® randomization or compliance. Mean body weights of the Ensure® sub-groups generally exceeded the ideal standard (Metropolitan Life, 1959), reflecting adequate energy reserves. Small fluctuations of means which are close to or exceed the ideal, as seen in Table 55, would not reflect significant change in nutritional status.

The proportion of patients in the depleted category, as defined in Table 35, was not assessed here due to the small number of patients meeting this criteria in some of the study groups. Arm measurement data were not available for these study groups.

C. Effects of Ensure® on Selected Laboratory Data

Selection of laboratory tests for Tables 56 and 57 was based on the principal factors analysis (Table 29) which identified the best estimates of general health. Several serum vitamin levels were also selected as reflecting changes in vitamin intake with Ensure® supplementation. Tables 56 and 57 show that the mean laboratory values for all study groups were well within the normal range at all time periods for all variables. The mean total lymphocyte count and serum vitamin B_{12} level decreased significantly from six months to twelve months ($p<0.05$) in NC. The mean serum vitamin B_{12} level also decreased significantly from six to twelve months in C and in NC+E ($p<0.05$)(Table 56). Mean serum vitamin B_{12} levels also decreased significantly ($p<0.01$) in the no Ensure® group and in the Ensure®-stopped group (Table 57). Changes in the laboratory means of these groups of patients consuming Ensure® do not reflect any consistent effects of this supplement. The proportions of patients outside the reference range were not assessed here due to the small number of patients categorized as "low" in some of the study groups.

D. Effects of Ensure® on the Crohn's Disease Activity Index

Table 58a shows the results of an analysis of covariance to assess the effects of Ensure® on the transformed Crohn's Disease Activity Index (√CDAI). Ensure® compliance was not accounted for in this initial analysis. Covariates were the √CDAI at the six month assessment, age, season of study entry and duration of disease. Main effects were counselling, Ensure®, sex and prior history of small bowel surgery. Reasons for the intuitive selection of these variables as covariates and main effects were given earlier. This table shows that, of the covariates, initial √CDAI and age accounted for a significant amount of variation. From six to nine months, Ensure® affected √CDAI with a significance of 10%. From six to twelve months, sex affected √CDAI at the same level of significance. Counselling and bowel surgery once again interacted significantly. The nature of the main effects on √CDAI is illustrated in Table 59. Ensure® was consistently associated with the lower √CDAI, a benefit that had a 10% level of significance in the six to nine month assessment period. The √CDAI of males was consistently lower than that of females, a difference that has a signifcance of 10% in the six to twelve month period.

Since compliance to Ensure® was poor, changes in the √CDAI were assessed after dividing the patients into groups according to the degree of compliance. These groups have previously been described in section 3A. Once again, these groups are defined as follows: 1. No

Ensure® - patients not randomized to Ensure®; 2. Ensure®, compliant - patients randomized to the Ensure® groups and who did not stop taking Ensure®; 3. Ensure®, stopped - patients randomized to the Ensure® group but who stopped consuming it at some point in time.

Figure 7 illustrates the unadjusted mean CDAI of the three groups of patients at each of the six, nine and twelve month assessment periods. There was a significant ($p<0.01$) decline in CDAI from 75 to 48, associated with the Ensure®-stopped group from six to nine months. Compliance to Ensure® did not produce significant benefits to the CDAI, though a drop in activity was seen (from 64 to 53). The group not randomized to Ensure® also showed a decrease in CDAI (from 99 to 86) but this was not significant. In the nine to twelve month period no significant changes were noted, although the no Ensure® and Ensure®-compliant group means maintained their decline while the mean CDAI of the Ensure®-stopped group increased.

The unexpected initial benefit of a low Ensure® intake, (that of the Ensure®-stopped group) relative to a more generous intake (that of the Ensure®-compliant group), was investigated more closely. Compliance to Ensure® was redefined in this analysis and randomization to C or NC was also accounted for. An analysis of covariance was done incorporating five counselling-Ensure® compliance groups: 1. counselling - not randomized to Ensure®; 2. counselling-compliant (consumed 50% to 100%) of the prescribed amount of Ensure®; 3. counselling-not compliant (consumed 0 to 49%) of the prescribed amount of Ensure®; 4. no counselling-not randomized to Ensure®; 5. no counselling-compliant; and 6. no counselling-not compliant. There was only one uncounselled patient taking at least 50% of the prescribed amount of Ensure®, so the no counselling-compliant category was omitted for purposes of this analysis. Table 60 shows that initial √CDAI and age accounted for significant amounts of variation. Of the main effects, Ensure® group and sex significantly affected the √CDAI from six to nine months, and from six to twelve months, respectively.

The nature of these effects is shown in Table 61. In the six to nine month period, patients in the counselling-not compliant group showed a tendency ($p<0.10$) to decrease their √CDAI relative to counselled patients not randomized to Ensure®. An unexpected observation is the reduction in √CDAI by the non-compliant counselled group relative to the compliant group in the six to nine month period. Though insignificant, this trend was explored further (in Table 62). In Table 61 in the uncounselled patients, the effects of Ensure® are insignificant but do show a trend to reducing the √CDAI. Table 61 also shows the lower √CDAI of males relative to females.

Further analyses of covariance were performed to investigate the above observation that the benefits of taking smaller amounts of Ensure® (i.e. less than 50% of prescribed cans) are greater than taking larger amounts (50% compliance or better). It is possible that benefits from Ensure® reach a plateau which is achieved at lower levels of intake than our 50% cut-off. Thirty-three percent and 25% of prescribed cans were used to redefine our compliant patients. Table 62 shows only the pertinent adjusted means from these analyses. Note that at these lower levels of compliance there is now a small number of patients in the no counselling-compliant group. At each of the 33% and 25% compliance levels, the only significant differences noted ($p<0.10$) were between the counselling non-compliant and no counselling-non-compliant groups in the six to nine month period. The lower √CDAI of the counselled group generally illustrates the benefits of counselling. At these lower compliance levels, however, we still observe that the √CDAI of the non-compliant counselled group was lower than that of the compliant group in the six to nine month period though this difference was not significant. In the uncounselled patients, the √CDAI of the compliant group is consistently lower than that of the non-compliant group and of the no Ensure® group, as expected.

Change in medications was investigated as a possible reason for the non-compliant counselled patients to show greater benefits than the compliant group. However, when the amount of medication was included as a covariate, the superiority of non-compliance was still evident, though insignificant, in the six to nine month period. This information was not incorporated into a table.

The reason for this unexpected trend is not clear. The amount of Ensure® consumed was calculated for each group using the 33% level of compliance by way of example. Compliant counselled patients consumed 1.9±0.6 cans per day in the six to nine month period; non-compliant counselled patients consumed 0.3±0.5 cans daily. Compliant uncounselled patients consumed 0.5±0.6 cans daily and non-compliant uncounselled patients consumed 0.4±0.6 cans per day. Why 0.3 cans of Ensure daily should benefit the counselled patients more than 1.9 cans is difficult to explain. Furthermore, the uncounselled patients benefitted from 0.5 cans but not 0.4 cans per day in the same time period.

Since the CDAI is a subjective assessment, a placebo effect of Ensure® was investigated. However, Tables 61 and 62 fail to reveal consistently higher √CDAI in the no Ensure® group.

E. Effects of Ensure® on Medication

Table 63 depicts the proportion of patients taking Prednisone and Salazopyrin® in each of the four counselling-Ensure® groups. Randomization to Ensure® did not significantly reduce the number of patients taking Prednisone. The need for Salazopyrin® therapy decreased markedly in the counselling group randomized to Ensure®, and in the no counselling group not taking Ensure. However these changes were not significant and all groups experienced at least some reduction in the use of Salazopyrin®.

Table 64 illustrates the effect of compliance to Ensure® on the need for drug therapy. The Ensure®-compliant group did show a decrease in the proportion of patients taking Prednisone and/or Salazopyrin®, but this decrese was not significant. The proportion of patients taking Salazopyrin® in the group not randomized to Ensure® also declined, but not significantly. The small amounts of Ensure® taken by the Ensure®-stopped group did not affect the taking of Prednisone or Salazopyrin®.

Analysis of covariance was done to investigate the effects of Ensure® on the dose of Prednisone and Salazopyrin® medication. This information was not incorporated into a table. The six counselling-Ensure® groups defined in Section D were again assessed. Thirty-three percent compliance was chosen for this analysis so that an uncounselled compliant group might be included (i.e. there were no uncounselled patients taking 50% or more of prescribed cans of Ensure®).

Of the main effects (Ensure® compliance group, sex and small bowel surgery), only sex significantly affected Prednisone dose ($p<0.05$). Ensure® did not have a significant effect on the dose of Prednisone. A significant interaction was found between the Ensure® compliance groups and a history of previous small bowel surgery ($p<0.05$). Females decreased their dose of Prednisone more than did males; this difference was significant ($p<0.05$) in the six to nine month period. No consistent trends are detected when studying the mean Prednisone dose of the various Ensure® compliance groups.

Regarding Salazopyrin®, none of the main effects (Ensure® compliance group, sex, small bowel surgery) had significant effects on the dose of this medication. Again, there was a significant interaction between the Ensure® compliance group and small bowel surgery ($p<0.05$). Patients with a history of small bowel surgery tended to have the higher dose of both Prednisone and Salazopyrin®, respectively, though this difference was not significant Doses of Salazopyrin® were similar for all Ensure® compliance groups and for males and females. Thus, no benefits of Ensure® were observed on the dose of medication consumed over a six month period.

F. Effects of Ensure® on Surgery, Hospital Admissions and Work Lost Due to Crohn's Disease

Table 65 depicts that Ensure® was associated with a slightly reduced percentage of patients needing surgery or admission to hospital in each of C and NC. The proportion of patients who required surgery was significantly lower in NC+E vs. NC ($p<0.05$) in the six to nine month period. Ensure® randomization was also associated with fewer days in hospital ($p<0.01$). The amount of work missed was less in counselled patients allocated to Ensure® over the six month period ($p<0.01$), but greater in the uncounselled group taking Ensure® ($p<0.01$).

Table 66 presents data where counselling effects have been ignored in order to compare the Ensure®-compliant and Ensure®-stopped groups versus no Ensure®. These groups have been previously defined. Randomization to Ensure®, regardless of compliance, was associated with reduced need for surgery and hospitalization. The proportion of patients in the Ensure®-stopped who entered hospital over the six month period was significantly lower than in the No Ensure® group ($p<0.01$). Total days in hospital were lower in the two groups taking Ensure® ($p<0.01$) than in the no Ensure® group. However, the length of hospitalization in the compliant group exceeded that of the non-compliant group ($p<0.01$). No consistent benefits from Ensure® could be observed in the amount of work missed. Relative to the Ensure®-stopped group, compliance to Ensure® was associated with a reduced amount of work lost over the six month period ($p<0.01$).

4. Summary of the Effects of Ensure®

1. Vitamin B_{12} intake was improved by compliance to Ensure®, but overall nutrient intake declined due to a decreased food intake.
2. No change in the percent ideal body weight
3. No benefits from Ensure® in selected laboratory means

4. Small amounts of Ensure® lowered the CDAI in the counselling group from six to nine months ($p<0.10$); no effect of Ensure® seen in the no counselling group.
5. No change in the proportion of patients taking Prednisone or Salazopyrin®, or in the dose of either medication.
6. Randomization to Ensure® was associated with a decreased need for surgery in the no counselling group ($p<0.05$) from six to nine months, a decreased length of hospitalization ($p<0.01$), and fewer work days lost in the counselling group only ($p<0.01$); lower amounts of Ensure® were associated with a reduced proportion of patients entering hospital in comparison to the group not randomized to Ensure® ($p<0.01$); larger amounts of Ensure® were associated with fewer work days missed ($p<0.01$), and both larger and smaller amounts of Ensure® decreased the length of hospitalization ($p<0.01$).

DISCUSSION

Diet therapy in Crohn's disease (CD) has traditionally consisted of the enteral or parenteral administration of dietary formulas. The aim of such therapy is to maintain adequate nutritional status while enforcing bowel rest. A role for diet as primary therapy in inflammatory bowel disease has been largely dismissed, or at least qualified as in this statement by LeLeiko (170): "It must be remembered...that only to the extent that improving nutrition allows for metabolic compensation and treats malnutrition, can nutritional therapy be considered primary therapy ." However, the role of diet in maintaining normal intestinal function (92) and immunocompetence (59) opens up the possibility that improving the nutritional status of patients with CD might affect the progress of the disease itself.

The only work to date which assesses the role of food in the treatment of CD was a retrospective study conducted by Heaton et al (123). A fiber-rich, unrefined-carbohydrate diet was prescribed to 32 out-patients with CD. Their clinical course over a mean of 52 months was compared with that of 32 matched control patients with CD receiving no dietary instruction. Hospital admissions were significantly fewer (11 vs 34, $p < 0.01$) and shorter (median 6 vs 15 days, $p < 0.02$) in the diet-treated group. A cumulative total of 111 days was spent in hospital by the diet group compared with 533 days by the control group ($p < 0.005$). Furthermore, whereas 5 control patients required intestinal surgery, only 1 diet-treated patient needed surgery over the course of the study. It was verified that the diet-treated patients were able to increase their dietary fiber intake and decrease their sugar intake. A mean dietary fiber intake of 33.4g per day was achieved in the diet group. This intake is approximately double that of the normal British population, but was not associated with an increased incidence of intestinal obstruction. However, no mechanism of benefit from the high fiber, low sugar diet was studied or suggested.

In contrast to Heaton's work, the present study was a prospective trial with a large number of patients (137) and randomly assigned diet and control groups. The dietary therapy of this study consisted not of a standardized dietary regime as in Heaton's work but, rather, individualized counselling. This individualized counselling aimed at normalizing each patient's nutritional status as estimated by their nutrient intake, anthropometric measurements and laboratory data. Dietary fiber and sugar intakes were adjusted only if they differed from those of the normal Canadian population.

However, like Heaton's study, the present study also reports the association of dietary therapy with improvements in the clinical course of CD. In the diet-treated group there was a decrease in the number of days spent in hospital and in time lost from work. There was also a reduction in Crohn's disease activity indices and a lowering of the amount of Prednisone and Salazopyrin® required to control the patients' disease activity.

I. The Effect of Counselling on Crohn's Disease Activity Indices and Clinical Course

Indices to assess disease activity have been widely used in therapeutic studies related to CD. In developing the original Crohn's disease activity index (CDAI)(26), the investigators selected eighteen parameters thought to indicate disease activity. Multiple regression with stepwise deletion eliminated all but eight variables which correlated most closely with the attending physician's over-all impression of the patient's status. Coefficients for each variable were computed to account for the differences in contribution of that variable to predicting the physician's evaluation. While the CDAI has been used in a large number of clinical studies (256)(268)(187), it is not universally accepted. This index is weighted heavily by a symptomatic component, despite the fact that symptoms of CD may not necessarily parallel inflammatory activity or pathological findings (134). For example, the diarrhea may be due to secondary lactase deficiency, bacterial contamination of the small bowel or bile salt wastage rather than being just a reflection of active disease. The CDAI has also been criticized as being cumbersome to calculate (27). Furthermore, subjective assessment of well-being and pain may comprise over a third of the final score. Modifications of the CDAI have been developed in an attempt to simplify its calculations, to reduce the subjective element and to incorporate laboratory measures of inflammatory activity (122)(269)(187)(9)(70)(63). None of the indices of disease activity, however, have been found to bear a prospective relation to the need for future abdominal surgery, the response to medical therapy or to the duration of remission, once it has been achieved (70). The term Crohn's Disease Activity Index may simply be a misnomer (134). Indeed, the team responsible for the development of the index have stated that they "wish we had called it an illness index"(239). The usefulness of such indices may be as an adjunct to radiological, endoscopic and laboratory examination to provide a comprehensive clinical impression of disease activity. The index is also of value in the assessment of a patient's overall well-being in response to a therapeutic regime.

In the present study, three indices were calculated to assess disease activity: the CDAI (26), a modification of this index by Harvey and Bradshaw (122), and the Oxford system of the International Organization for the Study of Inflammatory Bowel Disease (70). Approximately 70% of the study patients had inactive or mild disease at entry. A square root transformation of the CDAI (√CDAI) was found to best reduce the skewness resulting from this relatively healthy population (Table 27). This transformation also provided the advantage of reducing the wide range of values obtained (0-518), thereby facilitating statistical analysis. The Harvey and Bradshaw modified CDAI and the Oxford system were calculated in the present study in an attempt to reduce the subjectivity of the original CDAI and to eliminate any possible bias resulting from the non-blinded nature of the study design. The Oxford system was felt to be an insensitive measure of change in these relatively healthy patients, since the mean score at entry was only 1.7 out of a possible 9 (Table 44). Correlations among the √CDAI, the Harvey and Bradshaw modified CDAI and Oxford index were high (Figure 4). This is not surprising since all three reflect the same disease symptoms (diarrhea, abdominal pain and extraintestinal complications). Thus, each of the these three indices is likely reflecting the same endpoints. However, the √CDAI proved to be the best method of assesssing the clinical disease activity in the present study population. The range of this index was sufficiently wide to allow a sensitive assessment of clinical change. Statistical analysis of the change in this index with counselling was also facilitated by this index being a continuous rather than a discreet variable.

Diet counselling was associated with statistically significant decreases in all of these Crohn's disease activity indices (Tables 42 and 44). The most substantial decrease in the CDAI occurred during the first three months of counselling. This improvement was maintained throughout the remainder of the study, up to six months. The Harvey and Bradshaw modified CDAI and Oxford scores also decreased gradually so that by twelve months, the index values were significantly lower than at entry. It should be noted that those counselled patients without prior history of small bowel surgery showed the greatest decrease in CDAI (Table 42). This interaction may signify a diminished response to nutritional therapy after resection has reduced the functional bowel area.

The clinical significance of these decreases in the mean disease activity indices may be minimal since these means were in the range defined as inactive disease at all time periods. However, when selecting only those patients with an initial CDAI greater than 150 (denoting active disease), counselling was associated with a significant ($p < 0.05$) rate of remission (Table 43). Conversely, somewhat fewer counselled than uncounselled patients suffered a relapse of disease during the first six months of counselling. These results indicate a very real clinical benefit of counselling to attain and maintain remission of disease. Furthermore, this decline in CDAI was translated into a better quality of life for the patient with less medication, shorter hospitalization and less time lost from work.

The improvement in CDAI was associated with a reduced need for medication in the counselled groups (Tables 47 and 48). It is important to emphasize that the decline in CDAI was not due to increased drug therapy. This would have negated any benefits to CD attributed to counselling. The reduced need for Prednisone or Salazopyrin® to control disease activity is of particular significance since changes in medications were supervised by the attending physician, who was blinded as to the randomization of the patients into the counselling or no counselling arms of the study. It is reasonable to suggest, then, that diet counselling improved the clinical disease activity as well as the bowel inflammation.

Studies of nutritional support in inflammatory bowel disease have rarely followed changes in drug therapy. Dickinson et al (72) compared two treatment regimens (total parenteral nutrition vs. normal hospital diet) by the length of time necessary to reduce Prednisone to 10 mg/day in patients with acute ulcerative colitis or CD. The average time to reach this goal was not significantly shortened by TPN even though body protein reserves were maintained only in this group. Often hyperalimentation is initiated when standard medical, i.e. drug, therapy has failed to produce a satisfactory clinical response (167). This course of action signifies at least some potential for nutritional therapy as adjunctive primary therapy in CD.

Improvements in activity index scores also reflected an improved prognosis in the counselled patients in terms of fewer days in hospital and fewer days lost from work due to CD (Tables 45 and 46). However, a lowered incidence of surgery or frequency of hospital admissions was not associated with improvements in disease activity indices. Perhaps a longer-term follow-up is necessary to detect a potential benefit of counselling for these endpoints, since surgery is usually the last resort in treatment of active CD. De Dombal (70) has observed that the CDAI bears no relationship to need for surgery. The present study found that the mean CDAI of patients requiring surgery was higher than that of patients not needing surgery. However, there was considerable overlap of index values between the two groups and the differences were not statistically significant. Furthermore, many of the patients who required surgery met this need relatively early in the study, and perhaps the benefits achieved with diet counselling in the first three months were insufficient to prevent the complications leading to operation.

There is a paucity of prospective controlled studies defining the role of nutritional therapy in promoting recovery of surgical patients, in improving wound healing and resistance to infection or in reducing the length of convalescence (160), though such benfits are anticipated. Kushner and Craig (167) have summarized results of the numerous retrospective, generally nonrandomized studies where nutritional restitution through TPN and elemental diets achieve clinical remission and, frequently, delayed or averted surgery in patients with inflammatory bowel disease. Heaton et al (123) found that dietary instruction promoting a high fiber, low sugar regime to patients with CD was associated with fewer and shorter hospital admissions and a decreased need for surgery.

One mechanism for the benefits of nutrition repletion in CD is suggested by Harries et al (116)(117). These workers found that the inflammatory activity of CD, as measured by serum orosomucoid levels, regressed with enteral supplementation. Associated with improved anthropometric and laboratory measurements of nutritional status was evidence of recovery of cell-mediated immunity in these patients through an increase in T-lymphocyte count. They postulated that improved nutrition would be associated with improved cell mediated immunity and a better disease outcome. We did not perform measurements of T-cell function or orosomucoid levels in these patients. There were no clinical differences between the patients requiring surgery and those controlled medically. It is of interest to note, however, that the patients who responded best to diet counselling had not previously had small bowel surgery (Table 41). Nonetheless, it remains unclear why some patients failed to benefit from counselling and were subjected to surgery.

Except for the need for surgery, the overall effect of counselling, such as need for medication, was to improve the prognosis of those patients receiving dietary therapy. While counselling was associated with improvements in the patient's sense of well-being, as defined by the CDAI and other indices, such as time lost from work, it is especially encouraging to observe benefits to the more objective indicators of disease activity as well.

By studying the changes in nutrient intake, anthropometric measurements and laboratory data that occurred with counselling, one might be able to determine the mechanism by which diet therapy was able to improve the course of CD. The intakes of energy, fat and dietary fiber correlated inversely with the CDAI (Table 28), reflecting the well-known association of anorexia with active disease. The decreasing CDAI in the counselled group was associated with an improved intake of all nutrients (Table 33). This raises speculation on the cause and effect relationship between reduced disease activity indices and normalizing nutrient intake. Repletion of energy and protein as well as vitamin and mineral status can restore immunocompetence (168)(23) which, in turn, might alter the course of the disease (279). Adequate intestinal function might also be restored with improved nutrient status (15). Inadequate or excessive intakes of dietary fiber and unrefined carbohydrate, respectively, (the nutrients of interest in Heaton's work), as well as immoderate quantities of fat could aggravate disease symptoms. Excessively high sugar intakes by patients with CD have been reported frequently (191)(200)(152)(193)(265)(216). The present study found that neither grams of sugar per day nor sugar intake as a percent of calories were correlated with CDAI (Table 28). Brauer et al (42) found no difference in the sugar intake of female patients with CD compared to that of a female control group. The sugar intake of our female patients (104±62 g/day) was similar to that of the control group in the Brauer study (101±37 g/day). Hodges (130) found that the consumption by 47 patients with CD of foods primarily sugar and soft drinks was 22% and 48% less, respectively, than that reported by the Nutrition Canada survey. However, normal or even low mean intakes may still mask excessive intakes by a sub-group. The aim of counselling to normalize the consumption of all nutrients plus dietary fiber and sugar could account for the decline in disease activity index values seen in the present study.

Disease activity correlated significantly with a number of laboratory parameters. At study entry, the $\sqrt{\text{CDAI}}$ was significantly related to hemoglobin, hematocrit, serum iron, transferrin saturation, red blood cell count and volume, serum albumin and protein, serum zinc and serum red blood cell folate (Table 28). However, none of these laboratory tests showed a significant improvement to parallel the decrease in CDAI which occurred with counselling (Tables 37 and 38). Not even hematocrit and hemoglobin, which comprise one of the variables in each of the CDAI and Oxford index, respectively, reflected the improvement in disease activity. A variety of laboratory parameters have been thought to reflect CD activity, and have been incorporated into the various indices. In addition to hematocrit (26) and hemoglobin (70)(48)(63) are serum albumin (269) (186)(63) ESR (269)(48)(9), white blood count (48) and serum orosomucoid and C-reactive protein (9)(63). However, few of these laboratory measurements, except the acute phase proteins, are related purely to inflammatory activity. The majority probably relate more to symptoms or complications of the disease or to nutritional status, parameters which may change quite independently of inflammatory activity (134). The discrepancy between laboratory measures and the other parameters of nutritional and clinical status will be discussed later.

II. The Effect of Counselling on Nutrient Intake

We chose to use the 48-hour recall method from the numerous methods available for estimating nutrient intake. The ideal method of determining the habitual food intake of groups and of individuals has been widely discussed and actively debated (159). Food frequency questionnaires provide a record of foods consumed. They may be used to assess the composition and quality of the diet, but should not be used to predict the intake of individual nutrients (139)(205). In a food record, food intake is recorded, or weighed and recorded. A relatively accurate account of the nutrient intake may be calculated for those particular days. However, this method requires greater cooperation and motivation on the part of the participant. An additional drawback is that habitual food habits may be altered during the period of recording the food intake. This may arise if the patient attempts to adjust to any preconceived notion of what should be consumed. Dietary recall methods are frequently chosen to assess the nutrient intake of large groups. The 24-hour recall has been used in the Ten-State Nutrition Survey (1969-1970), the Nutrition Canada Survey (1970-1972) and the U.S. Health and Nutritional Examination Survey (HANES) (1971-1974). The major drawback to this method is the reliance upon the memory of the subject. While the recall method has limitations of interpretation at the individual level, it does provide a suitable means of obtaining the average intake of groups of 50 or more participants, as long as a 10% error is acceptable (289).

The 48-hour recall method was chosen for the present study in an attempt to minimize error due to day-to-day variation while not unduly taxing the memory of the subjects. The large numbers of patients in each study group (67 counselling, 70 no counselling) give us confidence in the mean nutrient intakes reported with this method. This method has been used previously (244)(130). Research has not been done to assess whether the 48-hour recall provides a more representative intake than a 24-hour recall or from two successive 24-hour recalls. Almost from the onset of the study, however, subjects recorded their intake for the two days previous to their visit to the clinic in order to facilitate this portion of the questionnaire. Based on a previous study where the between-person standard deviaton was 400 calories and the within-person standard deviation was 370 calories, Marr (190) has determined that a two-day food record will correctly classify the intake of 77% of subjects according to the total distribution of the group, while 1.5% of individuals will be grossly misclassified.

A criticism of all these dietary intake methods concerns whether an intake of one or more selected days is representative of an individual's habitual intake. Certain nutrients, such as vitamins A and C, have considerable day-to-day variaton (190). Furthermore, the "within-person" variability of daily nutrient intakes can be as large as the "between-person" variability for many nutrients (190). This variation limits the repeatability and validity of any one method in depicting habitual intake. While the individual food records of the counselled patients in the present study were interpreted with their limitations duly noted, these repeated monthly records supplied a valuable tool for individualized diet counselling, and habitual intakes quickly became apparent.

Nutritional deficiencies are a common complication of CD (131, 132)(240)(224). However, because the nutrient intake of patients with CD has not been well studied, the role of dietary intake in the development of the poor nutritional status of these patients remains undefined. Nutrient intake in CD may be reduced during active disease due to anorexia, fear of precipitating abdominal pain or diarrhea, altered taste, intolerance to certain foods such as milk or the inappropriate adherence to a low fiber diet. This was shown in the present study where the intake of energy, fat and dietary fiber were inversely correlated with $\sqrt{\text{CDAI}}$ (Table 28).

The nutrient intakes of the study patients, as a group, were generally satisfactory; that is, the means of all nutrients exceeded the 1980 American Recommended Dietary Allowance (RDA) except for folate in males and iron, calcium and folate in females (Table 9). However, for each nutrient there was a considerable proportion of patients consuming suboptimal intakes (Table 14). The nutrient intakes of the females were found to be generally poorer than those of the males. This poorer intake was due to the lower energy consumption of the females since, on a per 1000 kcal basis, the intake of the females was actually greater than that of the males for a number of nutrients (Table 12).

An investigation of 47 patients with CD at the University of Alberta (130) also found the mean nutrient intakes by both males and females to generally exceed recommended allowances (Appendix 7). In general, the mean nutrient intakes of that earlier study were similar to those in the present study. However, the intakes of preformed vitamin A and of vitamin B_{12} were considerably higher in the males in the present study. This may have been due to the increased consumption of certain foods in the present study, for example, liver, which contains large amounts of both preformed vitamin A and vitamin B_{12}. Despite normal mean intakes, Hodges noted a substantial proportion of patients with poor intakes. Less than 50% of male patients consumed the full recommended allowance for energy, vitamin A, vitamin B_6, and folate. Less than 50% of females consumed the full allowance for energy, calcium, iron, vitamin A, pantothenic acid, vitamin B_6, folate, vitamin B_{12}, and vitamin D. Using the same criteria in the present study, the same nutrients were poorly consumed by men and women, except for vitamin A (Tables 10 and 11). We do not present data on vitamin B_6, pantothenic acid or vitamin D intakes. Again, the greater consumption of certain vitamin A-rich foods by patients in our study could have contributed to this difference.

The literature contains a number of reports of suboptimal intakes by patients with CD. Kelts et al (156) found energy intake by CD patients to be lower than controls. However, normal intakes were observed by Thornton et al (265) and Mayberry et al (194). Intakes higher than controls were observed by Kasper et al (152). Differences among studies could be due to differences in Crohn's disease activity which may affect energy intake. The protein intake of CD outpatients has been determined in a number of studies: 80 g (194), 73 g (265), 89 g (152), and 86 g (130). These compare with 84 g in the present study. The protein intakes are generous in comparison to the RDA.

Other nutrients are frequently less well-consumed than energy and protein. Half or more of the CD patients studied by Linaker (175) and by Hughes and Williams (138) were consuming less than the RDA for vitamin C. This corresponds with approximately thirty percent of the patients in the present study who consumed less than the RDA. However, the range of vitamin C intakes in the present study was from 1 mg to 1212 mg (Table 32). None of the patients with CD assessed by Hoffbrand et al (135) or by Elsborg and Larsen (83) consumed the current standard of 200 µg free folate, and some consumed less than 50 µg, which is considered the minimum amount of folate necessary to prevent symptoms of deficiency (124). In the present study, 19% of patients at entry consumed less than 50 μg of free folate. However, 14% of patients also exceeded 200 μg of free folate. The reason for the wide range of vitamin C and folate intakes in the present study may be that a few foods are exceedingly rich sources of these nutrients while most contain only small amounts. Thus, the daily intake of either nutrient would fluctuate widely depending upon which foods were consumed.

Intakes of the no counselling group provide the first longitudinal investigation of nutrient intake by patients with CD. The intakes of this group remained fairly constant in the first six months of the study (Table 31), despite reporting to a dietitian at study entry and at the three and six month assessment periods. Obviously any need for alterations in the intake of these patients was not perceived by the patient, nor unconsciously indicated by the dietitian. The criteria for adequate nutrient intake in the present study was consumption of the full RDA. In the first six months, the magnitude of variation in the proportion of uncounselled patients meeting this criteria ranged from +18% for calcium (i.e. an increase of 18% above study entry in the proportion of patients meeting the full RDA) to -8% for vitamin A (i.e. a decrease in the proportion of patients) (Table 34). However, the vast majority of changes were within ±5%. These fluctuations probably reflect normal variation in the habitual intake of out-patients with CD, as well as the variability inherent in this method of dietary record/recall.

On the other hand, diet counselling was associated with an increase in the number of patients consuming the full RDA for all nutrients except iron and folate and energy in the entry to three month assessment period. These changes were almost consistently of a greater magnitude than those of the uncounselled group for the same nutrient. From entry to six months, these increases reached statistical significance for protein, riboflavin and vitamin C. A more detailed insight into these data is provided in Tables 33 and 34.

Recommended intakes for iron and folate have long been criticized as being unjustifiably high and unattainable, especially for women. The 1983 Recommended Nutrient Intakes for Canadians (RNI) acknowledges the discrepancy between a high occurrence of "sub-optimal" intakes and a low incidence of clinical signs of deficiency. These most recent standards substantially decrease the recommended intakes for folate and iron by approximately 50% and 21%, respectively, compared with the 1980 RDA. When using the proportion of patients consuming the full RNI as the criteria of change, counselling was associated with improvements in these nutrients as well. Thus, by counselling it was possible to improve the intake of all nutrients.

As a criteria of dietary adequacy, 2/3 RDA rather than the full RDA has also been used (39). These workers reasoned that since intake allowances are set at about two standard deviations above the median requirement for nutrients and at the median requirement for energy (158), and thereby exceed the requirements for the majority of individuals within the population, it seemed appropriate to use a value of less than 100% RDA as a standard of comparison. However, tables of recommended nutrient intakes are set to ensure against deficiency and provide adequate body reserves in a normal healthy population. Application of such standards to an unhealthy population, as in the present group of patients, can be made only if it is remembered that nutrient requirements during disease are unknown and, in fact, may be increased. We chose, therefore, to use the full RDA as the minimum criteria for an adequate intake. The recommended intake was raised for a specific patient if blood levels of that particular nutrient remained sub-optimal despite an intake consistently meeting the RDA.

The improved intake in response to counselling in the present study was gratifying. Those patients receiving counselling were generally highly motivated to modify their intake. There was a high level of knowledge of their disease and a keen awareness of their food intake as it affected gastrointestinal symptoms. The monthly counselling sessions probably further increased compliance to dietary suggestions, provided reinforcement and increased the degree of overall learning and nutritional knowledge. Motivation may have been further enhanced by the frequent observation that their CDAI and need for medication were decreasing. Whether these benefits of counselling on food intake continued after the end of the study is not known. The long-term effects of couselling in CD would constitute an interesting follow-up study.

III. The Effect of Counselling on Anthropometric Measurements

Anthropometric assessment is an accepted method of screening for protein-energy malnutrition (107), but this technique has been criticized as lacking the sensitivity to detect subtle changes in lean body mass (21). Furthermore, an active debate surrounds the appropriate standards to apply to individuals (32) and methods for classification of depletion (107). The present study uses the 1959 Metropolitan Life Insurance standards for body weight. These standards have the advantage of being the only weight standards that relate to mortality. The HANES I anthropometric data had been collected on what we felt to be the most representative population to date, at the time of the study, and, thus, provided the standard for the arm measurements. Body weight less than 85% of ideal, and arm measurements at the 5th percentile were the criteria for classifying a patient as depleted in energy or muscle reserve. During the course of the study, Canadian standards were made available, based on the Nutrition Canada Survey, and 1983 Metropolitan Life Insurance figures were released. The latest Canadian anthropometric standards are consistently lower than those provided by the HANES data. The 1983 Metropolitan Life figures for weight are higher than those provided in 1959. Application of these newer standards to our data would result in an increase in the proportion of patients classified as depleted for weight, and a decrease in those classified as depleted in the arm measurements.

Interpretation of arm measurements may be obscured in disease or therapy leading to fluid retention. Patients with CD often note a rapid weight gain when placed on Prednisone. While Blackburn and Thornton (34) maintain that the upper arm is usually spared edema, it is not known whether fluid accumulation associated with steroid therapy similarly spares the upper arm. The elevated mean triceps skin-fold measurements (TSF) seen in the present study might indicate that upper arm edema was present in many patients. In calculating the muscle circumference, presence of edema would result in an underestimation of protein status. The gradual decrease with time in mean skin-fold and in the proportion of protein-depleted patients (Table 35) does parallel the decrease in Prednisone taken by the counselled patients as the study progressed. However, the mean TSF also decreased in the uncounselled group where Prednisone therapy increased. Further investigation found that the mean of each anthropometric parameter for those patients taking Prednisone was almost identical to that of the group not taking Prednisone (Table 8). This similarity indicates that edematous or muscle wasting effects of steroid therapy were not evident in this study. While normal means may mask a subgroup of edematous or wasted patients, the similarity in standard deviation between the two groups indicates that such a subgroup probably did not exist to any greater extent in the group taking Prednisone than in the group not taking Prednisone. Thus, it appears to be valid to use arm measurements to assess energy and peripheral protein stores in patients taking Prednisone.

Anthropometric estimates of energy and protein status reflected a fairly healthy group of patients in the present study. Body weight and TSF means remained above ideal levels for the entire study, and the mean mid-arm circumference hovered just below ideal (Table 35). Hodges (130) also found that anthropometric means of 47 CD patients were close to or exceeding the ideal. However, for each measurement in the present study there were patients who qualified as being "depleted". Protein stores showed the greatest degree of depletion. Twenty percent of the study patients were at the 5th percentile for muscle circumference. Only 6% of patients fell in this range for TSF thickness, indicating generally adequate energy reserves in the group as a whole. Harries et al (115) found considerably larger numbers of CD patients at risk. In that study, the percentages of patients who were at risk of depletion, that is, below the 90% ideal standard for weight, mid-arm circumference, mid-arm muscle circumference and TSF thickness, were 20, 37, 35 and 51%, respectively. Though the criteria for depletion differ, it is obvious that there is a sub-group of patients with CD who have inadequate energy and protein reserves.

Changes in anthropometric means and in the proportion of depleted patients in the uncounselled group provide a longitudinal investigation into the normal fluctuations of this mode of nutritional assessment. The means, standard deviations and level of depletion in this group remained remarkably constant in the first six months of study, except for TSF. In this measurement, the mean dropped considerably after study entry. The proportion of depleted patients first increased, and then decreased. This trend may reflect a true reduction of arm fat, or a learning effect by the dietitians performing the measurements. The mean TSF also decreased substantially in the counselling group, but here the decline was associated with a reduced number of patients in the depleted category.

The anthropometric measurements did change in response to counselling and in association with an improvement in the CDAI. Relative to the uncounselled group, counselling was associated with a trend to decrease the proportion of depleted patients in the first six months (Table 35). The greatest benefits of counselling occurred with muscle circumference. The improved protein-energy status of the counselled patients by the six months assessment does parallel increases of 10% and 16% in the proportions of patients consuming the full RDA for energy and protein. Thus, anthropometric measurements performed serially may correctly reflect an improvement in energy and/or protein stores occurring in association with improved energy and protein intake. The effect of exercise on muscle mass was not assessed in this study. It is acknowledged that improved muscle circumference may have resulted not only from improved protein intake but also from increased exercise as the patients felt better.

IV. The Effect of Counselling on Laboratory Assessment

With the exception of transferrin saturation and the concentration of white cell vitamin C, the mean values of all the blood parameters at entry fell well within the reference range (Tables 16 and 17). The normal mean values, however, obscurred an abnormal sub-group: a substantial proportion of patients had suboptimal laboratory values for a number of measurements. A previous smaller study at this University with 47 outpatients with CD (130, 133) also found sizeable numbers of patients with low laboratory values. In that study, hemoglobin and hematocrit were low in 26% and 27%, respectively. Transferrin saturation was below the reference range in 59%, and serum ferritin levels were suboptimal in 9%. Serum levels of folate, vitamin B_{12} and carotene were low in 24%, 11% and 26%, respectively. The present study found the following proportions of patients with low laboratory values: hemoglobin - 7%, hematocrit - 5%, transferrin saturation - 57%, serum ferritin - 18%, serum folate - 10%, serum B_{12} - 4% and serum carotene - 20% (Tables 19 and 20). These two studies were well-matched for degree of disease activity.

Thus, some of the striking differences in proportions between these two studies may be attributed to different reference ranges.

The present study found low serum vitamin C and white cell vitamin C levels in 15% and 38% of patients, respectively (Table 17). Significantly more females than males had a low leukocyte ascorbate level. This may have resulted from use of the oral contraceptive agent in 17% of the females, or from different smoking habits. Though the patients in Linaker's study (175) had quiescent disease, their intakes of vitamin C were lower than in the present study. This difference in intake may account for the discrepancy in incidence of poor vitamin C status between the two studies. Linaker (175) noted low leukocyte ascorbic acid levels in 7 of 10 CD patients.

Low plasma retinol levels were found by Main et al (185) in 21% of patients with CD. However, in five outpatients, plasma retinol was only slightly reduced. In our study of 137 outpatients, none had a low serum vitamin A (Table 17). Serum vitamin A levels may only become abnormal after prolonged active disease with malabsorption of the fat-soluble vitamins. In the present study, low serum carotene levels were noted frequently (in 20% of patients), despite normal serum vitamin A levels. However, serum carotene measurements fluctuate with recent carotene intake. A habitually adequate preformed vitamin A intake despite a low carotene intake would account for the apparent discrepancy in this study.

Low serum vitamin B_{12} concentrations have been reported in 16% to 20% of CD patients (79)(62) resulting from bacterial overgrowth and ileal resection. In the present study serum vitamin B_{12} levels were low in only 4% of patients. Differences among the studies may be due to differing amounts of functional ileum in the patient populations. Folate deficiency, as measured by low serum and red cell folate levels and by megaloblastic anemia, is also frequent and well-documented in the literature (78)(62)(135)(83). Dyer et al (78) found megaloblastic changes attributable to folate deficiency in 24% of CD patients. In the present study, serum folate and red blood cell folate levels were low in 10% and 9% of patients, respectively (Table 17). This incidence of abnormal values is considerably less than many reports in the literature. However, reference ranges for serum folate levels, in particular, vary greatly from laboratory to laboratory and may partially explain the differences. Also the use of Salazopyrin® should be taken into account due to its interference with folate absorption.

Low serum zinc levels were found in over 40% of CD patients by McClain et al (196) as well as by Solomons et al (249). Low serum zinc correlated with low serum albumin in these studies. The present study found only 2% of patients had a low serum zinc, and there was no evidence of low serum albumin levels (Table 17). Zinc intakes were normal in McClain's study (196). They concluded that poor zinc status resulted from malabsorption. Thus, differences in the level of disease activity may contribute to the discrepancy in the incidence of zinc deficiency between this and other reports.

Thus, nutrient deficiencies are frequent and well-documented in CD. Differences among studies in the prevalence of reported deficiencies may be accounted for by variation in reference ranges, disease activity and site, nutrient intake, prescribed medications and perhaps even the ratio of males to females. It is also worth noting that even in the present study of outpatients with generally inactive disease, an abnormal sub-group exists for many laboratory measurements.

It had been expected that counselling would be associated with improved laboratory results, particularly since the recommended intake was set at an above-normal level if their laboratory value was suggestive of inadequate intake of a given nutrient. However, by the six month assessment, only transferrin saturation, total lymphocyte count, red blood cell count, alkaline phosphatase and serum vitamin C showed noticeable or consistent decreases in the proportion of counselled patients who had abnormal laboratory values (Table 39). On the other hand, in the uncounselled group during the same six month period, spontaneous improvements were seen in serum iron, transferrin saturation, total lymphocyte count, red blood cell count and mean red cell volume. Other laboratory parameters, in both groups, showed a tendency to worsen or remain unchanged. It must be assumed that these fluctuations in the uncounselled group reflect normal within-person variation inherent in laboratory assessment. It is also evident that, with this amount of normal fluctuation, counselling was not associated with any observable benefits to the laboratory status of these patients. Similarly, analysis of covariance found no influence of counselling on selected mean laboratory values. However, prior history of small bowel surgery was found to significantly reduce the mean laboratory values below those of patients not having had surgery. It appears that resection leaves long-lasting effects and intestinal adaptation may never fully compensate for loss of functional bowel area. Such an interaction also affected the response of the CDAI to counselling. Thus, a patient with no previous history of small bowel surgery is a better candidate for nutritional therapy than a patient who has had a resection.

It is difficult to explain why improvements in nutrient intake and anthropometric measurements, and benefits to the clinical course of the counselled patients were not associated with a greater normalization of laboratory indicators of nutritional status. Baker et al (14) have noted three drawbacks to the ability of any individual laboratory measurement of nutritional status to predict morbidity: 1. the difficulty in separating the effects of actual nutrient deprivation from the disease process in altering the measurement (i.e lack of specificity); 2. long half-lives, effective homeostatic control systems or abundant stores of some nutrients diminish the sensitivity of these measurements in both nutritional depletion and repletion; 3. the wide confidence limits of laboratory measurements due to normal variation within and between individuals, making them more suitable for use in epidemiological surveys than individual cases. Any of these points would interfere with the ability of laboratory values to adequately reflect other benefits associated with counselling. In CD, inflammation, infection, drug therapy and multiple concurrent nutrient deficiencies may all interfere with the final laboratory value. Clearly, then, laboratory values cannot be used by themselves to reflect the adequacy of changes in nutrient intake.

Kerr et al (158) have previously noted that the dietary recall data of the HANES report were of limited value in predicting laboratory values. In their study, dietary iron and dietary vitamin C correlated with hemoglobin and serum vitamin C levels, respectively, but other relationships were not significant. The authors attributed the poor correlations to circadian rhythms, fluctuations among age groups and between sexes, and the interplay of various diseases and hormones with blood levels of nutrients. In contrast, at entry in the present study, a number of correlations were found between nutrient intake and laboratory values (Table 28). Vitamin A intake correlated with serum vitamin A but not with serum carotene. Vitamin C intake correlated with serum vitamin C but not with white cell vitamin C. Iron intake correlated with both hemoglobin and hematocrit. However, the low correlation coefficients that were associated with each of these relationships means that such correlations are probably not relevant for prediction at the level of the individual patient. Thus, at least at study entry, nutrient intake and the appropriate laboratory measurements did correlate. The lack of correlation over time in these laboratory values and altered nutrient intake must have been due to other factors related to CD, such as malabsorption, drug therapy and increased requirements due to inflammation, fever or enteric losses.

Counselling was associated with substantial increases in the numbers of patients consuming the full RDA for vitamins A and C. However, the improvement in vitamin A intake could not be expected to greatly affect vitamin A status, as measured by serum vitamin A, since all counselling patients were above the reference range for serum vitamin A at all time periods. However, the mean serum vitamin A and serum carotene did increase with counselling. This possibly reflects a transition of serum values away from the low end of normal. The number of patients with a low serum carotene showed little change despite higher vitamin A intake. As expected, improved vitamin C intakes were reflected in a decrease in the number of patients with low serum vitamin C levels. Folate and iron intakes were shown to improve with counselling, using the more recent dietary standards, as previously described. The mean serum folate, while consistently well within the reference range, increased further during counselling, while mean red cell folate levels decreased. However, there was no change in the number of patients with low serum folate levels in the first six months of counselling. The number of counselled patients with a low red cell folate increased by the six month assessment. Finally, while iron intake improved in the counselled group, the proportion of patients with low levels of hemoglobin, hematocrit, serum iron and serum ferritin increased substantially. Only transferrin saturation reflected an improvement in the iron intake of these patients. The mean values of the group remained fairly constant. Only serum ferritin means decreased to any noticeable extent. This decrease could reflect either a drop in iron stores or a reduction in inflammatory activity which tends to elevate ferritin levels. The level of iron supplementation did not change appreciably over time, nor did the laboratory methodology for iron assessment alter throughout the course of the study. Therefore, we could find no explanation for the deterioration in iron status, which extended to the uncounselled group as well.

To clarify the role of laboratory assessment as a prognostic indicator, correlations were investigated between the CDAI and laboratory measurements. At entry, the transformed CDAI correlated inversely with various iron parameters, red blood cell count, mean red cell volume, serum albumin and protein and serum zinc, and positively with red cell folate. Of these, only improved red blood cell count paralleled the decline in CDAI in the counselled group. Since, the correlation coefficient values were very low, it is not surprising that changes in the CDAI with counselling in the individual were not well reflected by the laboratory values. Of the other correlating entry measurements, serum albumin, total protein and zinc levels may have shown improvement as disease activity subsided, but study patients almost consistently showed above normal values for these parameters at all time periods.

The positive relationship between CDAI and red cell folate levels might be explained by an increased folate supplementation prescribed by the attending physician to those patients with active disease. However, this relationship was also detected when we selected only those patients not receiving a folate supplement. It is possible that inflammation causes retention of tissue folate levels by a similar mechanism that elevates serum ferritin levels in the presence of active CD (176), though this is purely speculation.

A number of other laboratory levels also improved as disease activity decreased in the first six months of counselling. These levels were transferrin saturation, total lymphocyte count, alkaline phosphatase and serum vitamin C. Improvements in any of these tests might have implications in the progress of the disease itself. For example, a normalization of alkaline phosphatase resulting from decreases in the intestinal fraction of this enzyme could indicate a reduction of pathological processes in the gastrointestinal tract. A decrease in pericholangitis in these patients would also result in normalization of levels of the liver fraction of alkaline phosphatase. Improvements in transferrin saturation and vitamin C status could also have functional implications by way of helping to ensure adequate intestinal function (170) and immune response (59). Finally, improved total lymphocyte count could reflect recovery of cell-mediated immunity, mediated through improvements in nutritional status (116, 117). However, the uncounselled group also showed improvements in total lymphocyte count as well as in transferrin saturation during the time when the disease activity of this group was worsening. Thus, while improvements in certain laboratory values with counselling could illustrate a mechanism for the benefits of diet therapy in CD, in the present study the overall laboratory status of the counselling group did not improve relative to the no counselling group.

This study has not been the first to be unable to link laboratory data with other nutritional status or prognostic indicators of disease. As Hodgson (134) notes, laboratory measures often diverge from clinical assessments. That the relationships among nutrient intake, laboratory assessment and CD activity are tenuous by nature was illustrated by the principal factors analysis. The analysis identified no less than sixteen parameters which ranked the most highly with overall health (Table 29). The need for sixteen variables to completely assess health illustrates the complexity of this clinical entity and the relative independence of a number of health status measurements.

A mechanism by which counselling improved various clinical aspects of CD could not be traced to a specific nutrient or laboratory value. Measurements of C-reactive protein levels may have better reflected the benefits of counselling, and might have supplied the basis for a mechanism. Few of the laboratory tests performed in this study were sufficiently sensitive to indicate changes in biochemical function at the cellular level. It is the more subtle changes in gut function and immunocompetence that may have been altered by dietary counselling and which may have resulted in the observed clinical benefits.

V. The Effect of Ensure® Supplementation on Crohn's Disease

Defined formula diets (DFD) have a well-defined role as adjunctive medical therapy in the treatment of CD (167). These preparations have been found to be beneficial in a number of clinical situations relating to CD: 1. as primary therapy providing bowel rest in acute CD (270)(210); 2. in the management of enteric fistulae and partial bowel obstruction (222)(286)(54)(228); 3. to achieve preoperational nutritional rehabilitation, to minimize post-surgical complications and possibly delay surgery (50)(270)(222); 4. to aid in the control of diarrhea and steatorrhea (271)(228); and, 5. reversal of growth retardation in children and adolescents with CD (162)(164)(203). Thus, DFD have a major therapeutic role in the management of a number of complications of CD.

The physiological effects of DFD include a marked diminution of fecal bulk and frequency, a lessened stimulation of pancreatic and gastric secretion, alterations of fecal flora and a decrease in fecal bile acid excretion (169). A "medical bypass" situation is created, reducing potential pathogenic and antigenic components in the lumen and providing bowel rest for the affected area. However, the benefits of nutritional supplementation and repletion should not be overlooked, as most patients on a DFD regime gain weight and achieve positive nitrogen balance (116, 117)(270)(222)(164)(203). Harries et al (116) (117) postulated that nutritional repletion by DFD leads to the recovery of cell mediated immunity which enhances the patient's ability to suppress inflammation. Studies designed to address this question are currently in progress at the University of Alberta. Thus, there may be a role for DFD as primary therapy in CD.

In most studies assessing the therapeutic benefits of DFD, this constitutes the sole source of nutrition. However, some research, like the present study, has sought to supplement the oral intake with DFD. Kirschner et al (164) supplemented the diets of children with growth retardation due to CD. Low residue formulas were incorporated into the diet for three to twelve months in order to attain a caloric intake meeting the RDA. Ensure® or Vivonex® were chosen by individual taste preference, and these supplied an additional 600 to 1200 kcal/day. Restoration of linear growth was described, but the clinical courses of these children was not described, and details of the consumption of or compliance to the supplements were also not presented. Harries et al (116)(117) selected CD patients on the basis of malnutriton for study. Ensure Plus® was used for two months to four months to supplement each patient's normal diet to approximately 3000 kcal/day. The mean calories provided by the supplement was 555 per day. Improvements in anthropometric measurements, serum proteins, creatinine height index, circulating T lymphocyte numbers and serum orosomucoid levels were attributed to the higher energy intake. Cooke (294) has suggested that the dietary enrichment of other nutrients in the supplement might also have benefited these patients. However, a small study by Brignola et al (293) failed to show the magnitude of improvement seen by Harries et al (116, 117). Brignola and co-workers administered Precision® to a level of 10 kcal/kg ideal weight daily for two months to seven patients with CD. Anthropometric assessments improved slightly, but serum orosomucoids and CD activity did not indicate any clinical benefits of supplementation.

The present study also aimed for the incorporation of Ensure® as a supplement to the normal food intake. Supplementation of the order of 750 kcal/day for males and 500 kcal/day for females was attempted. Improvement in nutritional status was anticipated, and the progress of the disease was monitored in relation to these nutritional benefits. A high degree of anticipated tolerance and patient acceptability was the decisive factor in the choice of Ensure® for this study. This product is lactose-free, low in osmolality, low in residue, non-allergenic, ready-to-use, requires a minimum of digestion and was thought to be palatable. The patients were advised to consume it slowly and preferably chilled, either with a meal or as a between meal snack. Ideas for flavorings were suggested. The prescribed number of cans per day (three for men, two for women) was felt to provide a measurable nutrient supplement, yet one which would not interfere with their normal food intake.

Poor compliance to Ensure® was the major obstacle to the production of meaningful data in this portion of the study. Three and six months after randomization to Ensure®, 33% and 55% of patients, respectively, had stopped taking the supplement (Table 51). Of those who remained taking at least some Ensure®, the number of cans consumed per day was only 0.8 at each of nine and twelve months. Counselling did have a positive influence on compliance (Table 51). The mean number of cans consumed was higher with counselling, and fewer counselled patients stopped taking Ensure® over the six month period. Side-effects attributed to the consumption of Ensure® played a major role in determining whether a patient continued or stopped the supplement. In fact, of the seven patients who remained consuming the full prescribed number of cans of Ensure® until study completion, only one still complained of problems, that being diarrhea (Table 52). All seven patients in Brignola's study (293) were apparently able to tolerate the moderately large volume of recommended nutritional supplement. Seventeen percent of those studied by Harries et al (116) withdrew before the end of the trial due to profuse diarrhea attributed to Ensure Plus®, or because the patients found the supplement to be unpalatable.

The reason for the poor tolerability to Ensure® in the present study is not clear considering the efforts made by its manufacturers to enhance patient acceptance. Patients tended to drink the supplement faster than advised because many disliked the metallic aftertaste or the thick, "mucous-producing" consistency. Diluting the supplement was not readily accepted due to patient dislike of the flavor. Too rapid consumption could result in many of the intestinal complaints noted. It is possible that the poor compliance was due less to side-effects of consumption and more to the fatigue or lack of interest of being towards the end of a long-term study. At this later stage in the study, any further discomforts or infringes upon privacy or time would be less well tolerated. As a final explanation for the poor compliance, many patients randomized to Ensure® felt reasonably healthy and may have rebelled against anything "medicinal" at this time, since medications are so much a part of their lives during active disease. However, those patients who stopped taking Ensure® did so very soon after randomization. Thus, it is felt that, in most cases, side-effects to Ensure® were legitimate and of substantial severity to adversely affect the compliance of an otherwise well-motivated study group.

With so many non-compliant patients, it was not meaningful to investigate the Ensure® groups as randomized, other than to provide data for solely descriptive purposes. Categorizing the patients according to degree of compliance provided a more rational approach to the problem, but resulted in certain study groups containing very small numbers of patients.

1. The Effect of Ensure® on the Crohn's Disease Activity Index

The √CDAI was consistently lower in the group randomized to Ensure®, irrespective of compliance (Table 59). This effect was significant at the 10% level for the first three month assessment when the mean number of cans of Ensure consumed was 0.6 per day (150 kcal). Again, there existed an interraction between counselling and prior history of small bowel surgery. It has been observed that the effects of DFD in intestinal absorptive function differ between animals with an intact intestinal tract and those previously subjected to ileal resections (Thomson, unpublished observations, 1984). Again, there may be a diminished response to nutritional therapy with a reduced functional bowel area.

To determine if greater benefits to disease activity were derived from greater compliance to Ensure®, a series of investigations assessed compliance at three levels: those taking at least 50%, at least 33% and at least 25% of the prescribed number of cans of Ensure®. The energy supplement at each of these levels was 250, 167, and 125 kcal, respectively, for females, and 375, 250, and 188 kcal, respectively, for males. At each of the three levels of comparison, the uncounselled patients taking the most Ensure® had the lowest √CDAI (Tables 61 and 62). However, in the counselled group, the non-compliant patients consistently had the lowest √CDAI in the six to nine month assessment period. During the other time periods, the compliant counselled patients showed the greatest benefits of Ensure®. It is not clear why taking less Ensure® for the first three months is more benficial than taking more Ensure®. For example, when 33% of prescribed cans was the cut-off, the compliant counselled patients consuming 1.9±0.6 cans per day benefited less than the non-compliant group consuming 0.3±0.5 cans daily. Furthermore, compliant uncounselled patients consuming 0.5±0.6 cans per day benefited to a greater extent than non-compliant uncounselled patients drinking 0.4±0.6 cans daily.

It is possible that there is a plateau of effectiveness above which Ensure® ceases to be of benefit. The benefits of Ensure® may have reached a plateau at a relatively low level of intake. Most patients in this study were not severely sick or nutritionally depleted, so they were fed prophylactically rather than therapeutically. However, the benefits from Ensure® on disease activity seemed to occur at surprisingly low intake levels. The half can of Ensure® that appeared to benefit the uncounselled group, for example, contains 125 calories and supplements the food intake by only small fractions of the recommended nutrient intake standards. This level of supplement is considerably less than that found effective by Kirschner et al (164) or by Harries et al (116)(117). In fact, as will be described later, the quality of the diet, as determined by the proportion of patients consuming the full RDA, actually deteriorated with the addition of Ensure® (Tables 53 and 54).

There are suggestions in the literature that the specific amino acid and fatty acid composition of hyperalimentation formulas might impart beneficial properties over and above those of simple nutrient repletion. Jones et al (148) noted the superior nitrogen sparing effect of whole protein-containing versus elemental formulas. MacFie et al (295) have illustrated the specific effect of fat on repletion of lean body mass during parenteral nutrition of patients with metabolic stress. Morin et al (204) have found evidence that long chain triglycerides given intragastrically could be beneficial for the adaptive process of the remaining small bowel of laboratory animals with massive resection. Thus, it is possible that some as yet unidentified nutrient was present in the supplement which exerted a beneficial effect on the patient's symptoms. Replenishment of this substance was achieved with less than one can of Ensure® daily, and no further benefit was derived by the consumption of larger volumes of the supplement.

2. The Effect of Ensure® on Medications

Ensure® was associated with a decline in the proportion of patients taking medications in the various study groups (Tables 63 and 64). However, this decline was frequently observed in those groups not taking Ensure®, and could simply be attributed to reduced disease activity with the passage of time. Ensure® was also found to exert inconsistent effects on the dose of Prednisone and Salazopyrin®. In the uncounselled patients, Ensure® was not associated with a decrease in the dose of either medication compared to those not taking Ensure®. In the counselled patients, low amounts of Ensure® were associated with the lowest dose of Prednisone while, surprisingly, compliance was associated with the highest dose of Prednisone. Dose of Salazopyrin® was somewhat lower in patients taking Ensure®. However, these differences in doses did not reach even the 10% level of probability. Thus, the decreases previously noted in the √CDAI were not reflected by reduction in the dose of medication. We conclude that the small amounts of Ensure® consumed by these patients had no influence on the need for, nor the dose of medication needed to control disease activity.

3. The Effect of Ensure® on Surgery, Hospitalization and Work Lost due to Crohn's Disease

It was felt relevant to investigate this data only as a descriptive assessment in order to avoid making erroneous conclusions based on small numbers of compliant patients. Patients taking at least some Ensure® appeared to benefit by way of reduced incidence of surgery and fewer days spent in hospital (Table 65). This parallels the improvement seen in the √CDAI. However, the amount of work missed showed no obvious benefits from the supplement. Regardless of Ensure® randomization, patients receiving counselling experienced less surgery, fewer hospital admissions and less time spent in hospital and lost from work in the period six to nine months (Table 66). No benefits were associated with counselling during the final three months of study.

4. The Effects of Ensure® on Nutrient Intake, Body Weight and Laboratory Assessment

The amount of Ensure® prescribed was arbitrarily selected in the anticipation that it would not interfere with the quantity or quality of the food intake. Food supplements containing 1000 or 2000 calories have been given nightly to patients by tube for periods up to thirty-six days with no suppression of voluntary food intake (292). However, in the present study, the change in the numbers of Ensure®-compliant patients consuming the full RDA does not seem to reflect the addition of 0.8 cans of Ensure® daily (Table 54). Relative to the fluctuations in intake of the group not randomized to Ensure®, only an increase in vitamin B_{12} intake could be attributed to the consumption of Ensure®. It is apparent that nutrient intake from food declined during Ensure® consumption so that the overall quality of the diet did not improve. Counselling of those patients randomized to Ensure® did not appear to enhance the total nutrient intake.

We would not have expected 0.8 cans of Ensure per day to interfere with the food intake. The decrease in disease activity associated with taking some Ensure® might even have resulted in improved appetite. The patients noted that the Ensure® was very filling and a decrease in appetite was noted by a substantial proportion of patients. The bloating experienced by some would interfere with the capacity for food at the subsequent meal. Ensure® may have had less of an impact on daytime food intake if consumed just before bedtime, as was the regime in the study by Ashworth et al (1962).

The tendency in the Ensure® group to lower disease activity despite no obvious increase in nutrient intake makes this clinical improvement even more difficult to explain. As mentioned earlier, the specific amino acid or fatty acid formulation of Ensure® may have some as yet [illegible] bowel of patients with CD.

There were no significant changes in percent ideal body weight among the Ensure® groups (Table 55), although a few patients became non-compliant because of their perceived weight gain while taking Ensure. The means of selected laboratory parameters of patients taking Ensure® did not exhibit any changes relative to the random fluctuations of the group of patients not randomized to Ensure® (Tables 56 and 57). Thus, we were unable to show any benefits of taking small amounts of Ensure® on the parameters of nutritional status assessed in this study.

Thus, there is the suggestion in these data that taking at least small amounts of Ensure® may improve the clinical course of CD, although nutrient intake was not increased by Ensure® in the present study. Larger numbers of compliant patients are needed to assess whether Ensure® supplementation provides benefits equal to those observed by diet counselling.

SUMMARY OF FINDINGS

Diet counselling was associated with:

1. Increased nutrient uptake
2. Increased arm muscle circumference
3. No consistent effects on laboratory tests
4. Decreased indices of disease activity and increased incidence of disease remission
5. Decreased need for Prednisone and Salazopyrin® therapy
6. Decreased time spent in hospital and decreased amount of work lost

Compliance to Ensure® was poor, possibly due to a high incidence of side-effects attributed to taking Ensure®. No benefits were observed in nutrient intake, body weight or laboratory tests. However, certain trends were apparent:

1. Small amounts of Ensure®, but not larger amounts, were associated with a decrease in CDAI
2. Dose of medication was lower in counselled patients taking small amounts of Ensure®
3. Ensure® was associated with less surgery and reduced length of hospitalization.

CONCLUSIONS

1. Individualized diet counselling was shown to be of benefit to the clinical course of CD and, thus, may play an important role in the management of patients with this disease. While no one mechanism for this benefit was revealed, there was some evidence of improved nutritional status in counselled patients. Patients with no previous small bowel surgery responded best to counselling.

2. Attempts to supplement the food intake with Ensure® were largely unsatisfactory due to poor compliance. Small amounts of Ensure® did appear to be of some benefit to the clinical course of CD, though nutrient intake remained unchanged because of decreased food intake while consuming Ensure®. Thus, this study did not reveal conclusive data on the effects of Ensure®.

3. The nutritional status of out-patients with CD was observed at several time periods over six months, and was found to be generally satisfactory. However, there was a sub-group of patients at risk of depletion for a variety of nutrients. The extent of that risk varied with the measurement used to assess risk. For example, while protein consumption was typically generous, and serum albumin levels were within the normal range, a substantial number of patients had depleted muscle stores as assessed by arm muscle circumference. Changes over time in measurements of nutritional status in the uncounselled patients were generally small. Such changes would reflect normal

within-person variation inherent in the various assessment techniques, as well as day-to-day fluctuations in nutrient intake.

4. Significant correlations were observed among a variety of nutrient intakes but not among many laboratory values. Nutrient intakes generally correlated poorly with laboratory tests, but significant inverse correlations were noted between intake and disease activity and between laboratory tests and disease activity. However, the low correlation coefficients of most of these correlations means that such relationships may not exist in an individual patient.

SUGGESTIONS FOR FUTURE STUDIES

1. The design of future studies in CD should seek to avoid some of the limitations encountered in the present study. Patients should be matched for disease activity to avoid the possibility that it is easier to detect change if activity is high. To account for the possible psychological component of extra attention from more frequent assessments, the frequency of contact with study patients should be equal regardless of study group designation. Night supplementation may help reduce the effects of food intake observed by daytime consumption of dietary formulas and may improve compliance.

2. A follow-up assessment of these patients would be useful to determine the long-term effects of counselling on food intake and clinical course. It would also be of benefit to assess the minimum number of counselling sessions required to produce maximum benefit.

3. A food group analysis or a study of individual nutrients may reveal the component of the diet that is most beneficial to patients with CD.

4. Studies of changes in gut function and immunocompetence may determine the mechanism of the benefits achieved with dietary manipulation.

5. Dietary supplementation should be assessed in patients with active disease to facilitate compliance and to more easily detect benefits.

6. The effects of supplementation of a normal food intake should be compared to those of a supplement alone.

7. The effects of monomeric and polymeric diets on gut and immune function, and on drug absorption, should be evaluated and compared.

Table 1: Reasons for Patients not Completing Study

Reasons for Dropping Out	Counselling	No Counselling
Relocated	7	5
Became pregnant	1	1
Deceased	0	1
Unable to continue	2	0
TPN started	2	0
Unwilling to continue	2	0
Total	14	7

Table 2: Characteristics of Patients Who Completed Or Dropped Out of the Study

Patient Characteristic	Completed Study[1]	Drop-Outs[1]	
	(n=116)	0-6 months (n=12)	6-12 months (n=9)
Sex (M/F)	53M,63F	4M,8F	5M,4F
Counselling(C)/No Counselling(N)	53C,63N	8C,4N	6C,3N
Age (years)	33±11	33±13	28±10
Duration of known disease (years)	6.7±4.6	7.8±5.7	4.6±1.8
Crohn's Disease Activity Index	119±100	85±91	88±74
Length of small bowel resected(inches)	10±17	7±13	10±17
% ideal weight	103±18	112±23	101±14

[1] No significant differences noted between patients who completed study and those who dropped out

Table 3: Characteristics of Patients at Study Entry

Patient Characteristics	Males(n=62)		Females(n=75)		Counselling(M28,F39)		No Counselling(M34,F36)	
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Age at September 1,1981 (years)	32.2±9.5	17.5-58.6	34.6±11.8	19.9-71.0	35.5±12*	18.3-71.0	31.5±9.3*	17.5-60
Duration of disease	5.6±4.0*	0.5-14.3	7.4±5.0*	0.1-28.4	6.3±4.1	0.6-18.9	7.0±5.2	0.1-28
Crohn's Disease Activity Index	96±89	0-458	124±103	0-463	132±106*	0-463	92±84*	0-424
Length of small bowel resected (inches)	9±17	0-88	9±16	0-144	11±19	0-144	7±12	0-54
Percent ideal body weight	104±14	76-137	104±21	71-180	103±20	71-180	105±17	73-175
Smoking habits: current pack years	7.5±13.4 (n=28)	1.0-70.0	7.4±9.7 (n=41)	2.0-40.0	7.2±12.4	2.0-70.0 (n=31)	7.6±10.6	1.0-4 (n=39)
Previous pack years	4.6±7.9 (n=13)	1.0-26.0	5.2±8.3 (n=17)	1.0-30.0	5.8±8.8	1.0-26.0 (n=16)	3.9±7.0	1.0-3 (n=14)

* Means significantly different for males vs. females, and for counselling vs. no counselling

Table 4: Characteristics of Patients at Study Entry

Patient Characteristics	Males (n=62) (%)	Females (n=75) (%)	Counselling (n=67) (%)	No Counselling (n=70) (%)
Site of Crohn's disease: small bowel only	34	32	39	27
large bowel only	5	9	7	7
small and large bowel	61	59	54	66
Site of surgery: small bowel	45	43	42	46
large bowel	34	42	34	41
kidney	2	3	4	2
gall bladder	13*	2*	2*	12*
perianal	10	14	14	10
Ileostomy/colostomy	5	6	6	5
Renal calculi	9	6	8	6
Metabolic bone disease	2	8	5	5
Ankylosing spondylitis	12	-	7(males)	5(males)
Intolerant to milk	16	27	25	19
Taking vitamin/mineral supplements	48	51	52	42

* Proportions significantly different for males vs. females, and for counselling vs. no counselling ($p<0.05$)

Table 5: Medications taken by Patients at Study Entry

Medication	Total Patients (n=137) %	Counselling (n=67) %	No Counselling (n=70) %
Prednisone	42	48	36
Salazopyrin®	47	42	53
Prednisone & Salazopyrin®	20	21	20
Imuran	4	5	3
Flagyl®	12	10	13
Other antibiotics	15	16	14
Lomotil®/Codeine/Imodium®	21	25	17
Questran®	4	6	1
Metamucil®	7	9	4
Oral Contraceptives (females)	17	21	14

Table 6: Medications Taken Compared to Site of Crohn's Disease

Medication	Site of Crohn's Disease		
	Small bowel only (n=45)	Large bowel only (n=10)	Small & large bowel (n=82)
Prednisone	42[1]	40[1]	41[1]
Salazopyrin®	40	60	50
Imuran	4	10	2
Flagyl®	13	30	9
Other antibiotics	20	10	13
Lomotil®/Codeine/Imodium®	20	10	23
Questran®	0	10	5
Metamucil®	4	10	7

[1] Data presented as proportion of patients in each group taking medication

Table 7: Anthropometric Data of Patients at Study Entry

Anthropometric	Males(n=62)		Females(n=75)		Counselling(n=67)		No Counselling(n=70)	
Measurement(% ideal)	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Body weight	104±14	76-137	104±21	71-180	103±20	71-180	105±17	73-175
Mid-arm circumference	96±10*	75-116	100±15*	64-157	96±14	64-157	99±12	74-137
Triceps skin-fold$^{a@}$	127±68	33-300	122±45	29-260	118±58	29-300	130±54	33-278
Fat area^{a}	121±66	29-285	122±61	20-372	114±67	20-372	129±60	28-280
Muscle circumference^{b}	92±8	76-112	93±10	67-123	92±10	67-123	93±9	77-122
Muscle area^{b}	84±17	31-125	88±19	56-151	84±18	31-151	87±18	56-148

* Means significantly different for males vs. females ($p<0.05$)
@ Anthropometric parameters followed by the same letter (a-a, or b-b) are significantly correlated ($p<0.01$)

Table 8: Effects of Prednisone on Anthropometric Measurements

Anthropometric Measurement (% ideal)	Taking Prednisone (n=57)[1] Mean ± SD	Not taking Prednisone (n=80)[1] Mean ± SD
Weight	102 ± 18	105 ± 19
Mid-arm circumference	97 ± 13	98 ± 14
Triceps skin-fold	124 ± 59	125 ± 56
Muscle circumference	93 ± 10	92 ± 9
Muscle area	87 ± 19	85 ± 17
Fat area	121 ± 63	124 ± 66

[1] No significant differences noted between patients taking and not taking Prednisone

Table 9: Mean Nutrient Intake at Study Entry of Patients with Crohn's Disease Compared with Intakes from Nutrition Canada

Nutrient[1]	Patients with Crohn's Disease		Nutrition Canada[2]	
	Males(n=62) Mean ± SD	Females(n=75) Mean ± SD	Males Mean	Females Mean
Energy (kcal)	2932±970	1775±667	3349	1946
Protein (g)	108 ± 36	65 ± 27	124	75
Fat (g)	125 ± 51	77 ± 34	155	88
Carbohydrate (g)	334 ± 122	205 ± 96	337	207
Crude Fiber (g)	4.7 ± 2.4	3.3 ± 2.0	4.8	3.2
Dietary Fiber (g)	18.4 ± 11.1	12.2 ± 7.9	-	-
Calcium (mg)	992 ± 506	790 ± 736	1189	788
Phosphorus (mg)	1634 ± 552	1089 ± 619	-	-
Iron (mg)	18.0 ± 6.3	11.2 ± 4.8	19	12
Vitamin A (IU)	8096 ± 9701	5463 ± 6265	-	-
Carotene (IU)	3402 ± 3224	2785 ± 2775	-	-
Preformed Vitamin A (IU)	5036 ± 8976	2874 ± 5271	-	-
Thiamin (mg)	1.7 ± 0.8	1.0 ± 0.5	1.7	1.1
Riboflavin (mg)	2.5 ± 1.3	1.7 ± 1.3	3.0	1.8
Niacin (mg)	41.4 ± 13.8	24.0 ± 10.3	-	-
Vitamin C (mg)	175 ± 174	104 ± 96	114	90
Vitamin B_{12} ()g)	8.1 ± 14.4	4.8 ± 8.1	-	-
Free Folate ()g)	145 ± 95	97 ± 74	-	-
Total Folate ()g)	236 ± 105	155 ± 90	226	145
Sugar (g)	171 ± 81	104 ± 62	-	-
Cholesterol (mg)	529 ± 339	292 ± 186	-	-

[1] Nutrient intake means of the present study do not include vitamin/mineral supplements; each intake value of the present study is the mean of two days

[2] Mean intake of prairie adults (20-39 years), Bureau of Nutritional Sciences, Health Protection Branch: Nutrition: A National Priority. Department of National Health and Welfare, Ottawa, 1973

Table 10: Proportion of Male Patients with Crohn's Disease Meeting The Recommended Daily Allowances (RDA) at Entry

	Proportion of Intakes Meeting Allowances[1]			
Nutrient	Full RDA[2]	2/3 RDA	1/2 RDA	1/3 RDA
Energy (kcal)*	48	94	100	100
Protein (g)*	97	100	100	100
Calcium (mg)*	58	69	92	100
Phosphorus (mg)*	97	100	100	100
Iron (mg)*	92	100	100	100
Vitamin A (IU)	55	77	87	95
Thiamin (mg)*	60	95	100	100
Riboflavin (mg)*	81	97	100	100
Niacin (mg)	100	100	100	100
Vitamin C (mg)	82	89	90	97
Vitamin B_{12} (μg)*	74	89	97	100
Total Folate (μg)*	8	31	60	81

[1] Proportions calculated from the food intakes of 62 males; vitamin/mineral supplements are not included

[2] From Recommended Dietary Allowances, Revised 1980. Food & Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

* Significant difference between males and females (Table 11) in the proportion of intakes categorized into the RDA categories ($p<0.05$)

Table 11: Proportion of Female Patients with Crohn's Disease Meeting the Recommended Daily Allowances (RDA) at Entry

Nutrient	Proportion of Intakes Meeting Allowances[1] Full RDA[2]	2/3 RDA	1/2 RDA	1/3 RDA
Energy (kcal)*	34	75	78	100
Protein (g)*	77	96	99	100
Calcium (mg)*	32	56	75	85
Phosphorus (mg)*	64	89	96	99
Iron (mg)*	16	40	61	91
Vitamin A (IU)	51	68	79	92
Thiamin (mg)*	47	77	91	95
Riboflavin (mg)*	60	84	95	95
Niacin (mg)	92	96	100	100
Vitamin C (mg)	63	73	84	89
Vitamin B_{12} (μg)*	49	65	75	88
Total Folate (μg)*	4	12	23	51

[1] Proportions calculated from the food intakes of 75 females; vitamin/mineral supplements are not included

[2] From Recommended Dietary Allowances, Revised 1980. Food & Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

* Significant difference between females and males (Table 10) in the proportion of intakes categorized into the RDA categories ($p<0.05$)

Table 12: Nutrient Density of Intake at Entry[1]

Nutrient	Males (n=62)	Females (n=75)
Protein (g)	37	36
Fat (g)	43	43
Carbohydrate (g)	114	115
Crude Fiber (g)	1.6	1.8
Dietary Fiber (g)	6.3	6.8
Calcium (mg)	337	442
Phosphorus (mg)	556	610
Iron (mg)	6.1	6.3
Vitamin A (IU)	2753	3059
Carotene (IU)	1157	1560
Preformed Vitamin A(IU)	1712	1609
Thiamin (mg)	0.6	0.6
Riboflavin (mg)	0.9	1.0
Niacin (mg)	14.1	13.4
Vitamin C (mg)	60	58
Vitamin B_{12} (μg)	2.8	2.7
Free Folate (μg)	49	54
Total Folate (μg)	80	87
Sugar (g)	58	58
Cholesterol (mg)	180	164

[1] Nutrient intake per 1,000 kcal

Table 13: Nutrient Intakes of the Counselling and No Counselling Groups at Study Entry (Mean ± SD)

Nutrient[1]	Counselling (n=67)	No Counselling (n=70)
Energy(kcal)	2262 ± 1042	2327 ± 948
Protein(g)	81 ± 41	87 ± 35
Fat(g)	96 ± 51	101 ± 46
Carbohydrate(g)	262 ± 128	263 ± 122
Crude Fiber(g)	3.8 ± 2.2	4.1 ± 2.3
Calcium(mg)	842 ± 743	928 ± 595
Phosphorus(mg)	1289 ± 711	1387 ± 622
Iron(mg)	14.6 ± 7.3	13.9 ± 5.7
Vitamin A(IU)	6956 ± 10,365	6390 ± 6155
Thiamin(mg)	1.4 ± 0.9	1.2 ± 0.6
Riboflavin(mg)	2.2 ± 1.7	2.0 ± 1.2
Niacin(mg)	31.3 ± 16.0	32.4 ± 13.6
Vitamin C(mg)	150 ± 170	121 ± 109
Vitamin B_{12}(μg)	7.2 ± 15.3	5.4 ± 8.4
Total Folate(μg)	198 ± 116	184 ± 95

No significant difference in mean intakes between counselling and no counselling

[1] Intake of vitamin or mineral supplements not included

Table 14: Proportion of Patients in the Counselling and No Counselling Groups Meeting the Recommended Daily Allowances (RDA) at Study Entry

Nutrient[1]	RDA[2]	Counselling n=67	No Counselling n=70
Energy (kcal)	Full	43	39
	2/3	83	85
	1/2	86	91
	1/3	100	100
Protein (g)	Full	79*	93*
	2/3	96	100
	1/2	99	100
	1/3	100	100
Calcium (mg)	Full	42	46
	2/3	60	64
	1/2	82	83
	1/3	94	90
Phosphorus (mg)	Full	78	80
	2/3	93	96
	1/2	96	100
	1/3	99	100
Iron (mg)	Full	52	49
	2/3	66	69
	1/2	75	83
	1/3	96	94
Vitamin A (IU)	Full	49	56
	2/3	72	73
	1/2	79	86
	1/3	91	96
Thiamin (mg)	Full	58	47
	2/3	84	87
	1/2	93	97
	1/3	96	99
Riboflavin (mg)	Full	69	70
	2/3	88	91
	1/2	97	97
	1/3	97	97
Niacin (mg)	Full	93	99
	2/3	96	100
	1/2	100	100
	1/3	100	100
Vitamin C (mg)	Full	72	71
	2/3	81	80
	1/2	85	89
	1/3	91	94
Vitamin B_{12} (μg)	Full	57	64
	2/3	73	79
	1/2	82	87
	1/3	90	94
Total Folate (μg)	Full	9	3
	2/3	25	16
	1/2	45	34
	1/3	61	67

[1] Vitamin/mineral supplements are not included

[2] From Recommended Dietary Allowances, Revised 1980. Food & Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

* Significant difference between counselling and no counselling in the proportion of patients consuming the full RDA for protein ($p<0.05$)

Table 15: Pearson Correlation Coefficients Between Selected Nutrient Intakes

Nutrient Intakes	r value	r^2 value
Protein & iron	0.73**	0.53
Protein & niacin	0.94**	0.88
Protein & vitamin B_{12}	0.25**	0.06
Protein & preformed vitamin A	0.19*	0.04
Iron & thiamin	0.70**	0.49
Iron & niacin	0.79**	0.62
Iron & folate	0.53**	0.28
Calcium & riboflavin	0.81**	0.65
Calcium & phosphorus	0.88**	0.77
Vitamin C & folate	0.71**	0.50
Vitamin C & vitamin A	0.18*	0.03
Vitamin C & carotene	0.22**	0.05
Vitamin C & dietary fiber	0.16*	0.03
Crude fiber & dietary fiber	0.80**	0.64

* Correlation coefficient significant ($p<0.05$)

** Correlation coefficient significant ($p<0.01$)

Table 16: Hematological Data of Patients with Crohn's Disease at Entry

Hematological Test	Mean±SD	Range		Proportion of Patients Outside Reference Range[1]		Reference Range[2]
				Males (n=62)	Females (n=75)	
Hemoglobin(g/dl)	14.1±1.5	9.8-17.8		10	3	M:13-17;F:11-16
Hematocrit(%)	41±4	32-52		6	3	M:38-50;F:34-46
Serum iron()g/dl)	65±35	12-187		52	39	M:65-145;F:50-130
Serum ferritin(ng/ml)	78±85	0-424				
			high	0*	9*	
			low	24*	11*	M:25-465;F:15-200
Transferrin saturation(%)	20±12	4-60		52	61	20-45
Total iron binding capacity ()g/dl)	326±62	171-507				
			high	3*	14*	
			low	11	9	250-400
White blood cell count(/mm^3)	8.3±2.5	4.1-17.9		0	0	4.0-9.0
Total lymphocytes(/mm^3)	1703±769	370-4389		48	47	1500-3500
Red blood cell count(/mm^3)	4.7±0.5	3.3-5.8		8**	28**	4.3-5.7
Mean red cell volume()^3)	89±6	73-106				
			high	2*	12*	
			low	23	13	83-97
Prothrombin time(%)	98±5	87-116			0	0120

[1] Patients recorded are those with values lower than the stated reference range, except for prothrombin time which records those greater than the reference value. Both extremes are noted for some parameters.

[2] Reference range at the Department of Laboratory Medicine, University of Alberta, 1980.

*,** Significant difference between males and females in the proportion of patients outside the reference range, p<0.05, and p<0.01, respectively

Table 17: Biochemical Data of Patients with Crohn's Disease at Entry

Biochemical Test	Mean ± SD	Range	Proportion of Patients Outside Reference Range[1] Males (n=62)	Females (n=75)	Reference Range[2]
Serum albumin (g/dl)	4.1 ± 0.4	3.0-6.1	0	0	3.0-4.8
Serum protein (g/dl)	6.9 ± 0.5	4.1-8.7	3	0	5.8-8.0
Creatinine height index (%)	103 ± 34	7-184	32	38	90
Serum calcium (mg/dl)	9.2 ± 0.4	8.1-10.2	0	0	8.0-10.2
Alkaline phosphatase (IU/l)	90 ± 39	40-325	21	17	40 - 110
Serum magnesium (mg/dl)	1.9 ± 0.2	1.0-2.4	3	1	1.7-2.6
Serum phosphorus (mg/dl)	3.3 ± 0.6	1.7-4.8	8	3	2.5-4.8
Serum vitamin A (μg/l)	659 ± 207	310-1480	0	0	300-900
Serum carotene (μg/dl)	78 ± 42	5-323	16	24	50-50
Serum zinc (μg/dl)	88 ± 16	52-140	2	1	60-150
Serum copper (μg/dl)	135 ± 44	61-308	3	1	70-140
Serum folate (ng/ml)	4.5 ± 5.6	0.8-54.5	11	9	1.7-8.6
Red cell folate (ng/ml)	617 ± 561	109-4743	5	13	245-971
Serum B_{12} (pg/ml)	357 ± 170	63-999	3	4	140-520
Serum vitamin C (μmol/l)	63 ± 29	11-171	11	18	30-85
White cell vitamin C (μmol/10^9)	0.7 ± 0.3	0.2-1.5	26**	49**	0.7-1.7

1 Patients recorded are those with values lower than the stated reference range, except for alkaline phosphatase which records those greater than the reference range.

2 Reference range at the Department of Laboratory Medicine, University of Alberta, 1980.

** Significantly more females than males have a low white cell vitamin C ($p<0.01$)

Table 18: Hematology and Biochemistry Values of
the Counselling and No Counselling Groups
at Study Entry (Mean ± SD)

Laboratory Test	Counselling (n=67)	No Counselling (n=70)
Hemoglobin(g/dl)	14.1±1.4	14.1±1.6
Hematocrit(%)	41.1±3.4	41.3±4.1
Serum iron(μg/dl)	67±34	63±37
Serum ferritin(ng/ml)	80±84	76±86
Transferrin saturation(%)	21±11	20±12
Total iron binding capacity(μg/dl)	328±65	324±59
White blood cell count(mm^3)	8.3±2.8	8.2±2.6
Total lymphocytes($/mm^3$)	1633±661	1771±859
Red blood cell count($/mm^3$)	4.6±0.5	4.7±0.5
Mean red cell volume(μ^3)	89±6	88±7
Prothrombin time(%)	99±5	97±5
Serum albumin(g/dl)	4.1±0.4	4.1±0.4
Serum protein(g/dl)	7.0±0.5	6.9±0.6
Serum calcium(mg/dl)	9.3±0.4	9.2±0.4
Alkaline phosphatase(IU/l)	88 ±47	91±30
Serum magnesium(mg/dl)	2.0±0.2	1.9±0.2
Serum phosphorus(mg/dl)	3.2±0.6	3.4±0.6
Serum Vitamin A(μg/l)	674±204	645±210
Serum carotene(μg/dl)	85±50	72±31
Serum zinc(μg/dl)	90±16	86±15
Serum copper(μg/dl)	141±52	130±34
Serum folate(ng/ml)	4.3±3.9	4.7±6.9
Red cell folate(ng/ml)	688±711	549±357
Serum B_{12}(pg/ml)	373±193	341±144
Serum vitamin C(μmol/l)	61±26	65±31
White cell vitamin C ($\mu mol/10^9$)	0.7±0.3	0.7±0.3

Table 19: Proportion of Counselling and No Counselling Patients Outside of Reference Range[1,2] at Study Entry: Hematological Data

Hematological Test		Counselling (n=67)	No Counselling (n=70)
Hemoglobin(g/dl)		5	8
Hematocrit(%)		2	8
Serum iron(µg/dl)		37	53
Serum ferritin(ng/ml)[3]	high	4	6
	low	17	19
Transferrin saturation(%)		53	60
Total iron binding capacity(µg/dl)	high	11	7
	low	11	10
White blood cell count(/mm^3)		1	0
Total lymphocytes(/mm^3)		46	48
Red blood cell count(/mm^3)		23	16
Mean red cell volume(%)	high	6	9
	low	12	23
Prothrombin time(%)		0	0

[1] Refer to Table 16 for reference range.

[2] Patients recorded are those with values lower than the stated reference range, except for prothrombin time which records those greater than the reference value. Both extremes are noted for some parameters.

Table 20: Proportion of Counselling and No Counselling Patients Outside of Reference Range[1,2] at Study Entry: Biochemical Data

Biochemical Test	Counselling (n=67)	No Counselling (n=70)
Serum albumin (g/dl)	0	0
Serum protein (g/dl)	1	1
Creatinine height index (%)	32	41
Serum calcium (mg/dl)	0	0
Alkaline phosphatase (IU/l)	16	21
Serum magnesium (mg/dl)[3]	3	1
Serum phosphorous (mg/dl)	9	1
Serum vitamin A (μg/l)[3]	0	0
Serum carotene (μg/dl)	22	19
Serum zinc (μg/dl)	1	1
Serum copper (μg/dl)	1	1
Serum folate (ng/ml)	10	10
Red cell folate (ng/ml)[3]	9	10
Serum B_{12} (pg/ml)[3]	4	3
Serum vitamin C (μmol/l)	17	13
White cell vitamin C (μmol/10^9)[3]	37	37

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[1] Refer to Table 17 for reference range

[2] Patients recorded are those with values lower than the stated reference range, except for alkaline phosphatase which records those greater than the reference range.

Table 21: Proportion of Patients with Laboratory Values Lower than Selected Reference Ranges at Study Entry

Laboratory Test		Lower limit of reference range	Proportion of patients
Hemoglobin (g/dl)	male:	13*	10
		12	6
	female:	12	7
		11*	3
Serum albumin (g/dl)		3.5	6
		3.0*	0
Serum folate (ng/ml)		3.5	62
		3.0	45
		2.5	30
		1.7*	10
Serum vitamin C (μmol/l)		40	19
		30*	15
White cell vitamin C (μmol/10^9)		0.7*	37
		0.6	25

* Indicates lower limit of reference range at the Department of Laboratory Medicine, University of Alberta, 1980.

Table 22: Pearson Correlation Coefficients among Selected Hematology and Biochemistry Data

Laboratory Data	r value	r^2 value
Serum folate and red cell folate	0.43**	0.18
Serum vitamin C and white cell vitamin C	0.11	0.01
Serum iron and serum ferritin	0.00	0.00
Serum carotene and serum retinol	0.07	0.00

** Correlation coefficient signifcant ($p<0.01$)

Table 23: Urinary Data of Patients at Study Entry

			Proportion of Patients Exceeding Reference Range[1]		
Urinary Test	Mean ± SD	Range	Males (n=25)	Females (n=35)	Reference Range
Urinary creatinine (g/TV[2])	1.3±0.4	0.3-2.1	32	20	M:1.0-1.7; F:0.9-1.4
Urinary urea nitrogen (g/TV)	8.9±3.5	2.2-18.2	-	-	-
Urinary oxalate (mg/TV)	22.0±15.6	4.0-99.0	8	9	10 - 40
Urinary phosphorous (mg/TV)	868±381	159-1742	48	31	0 - 1000
Urinary calcium (mg/TV)	146±107	13-422	36	17	50 - 200

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[1] Reference range at the Department of Laboratory Medicine, University of Alberta, 1980.

[2] TV is total volume (volume per 24 hours)

Table 24: Fecal Data of Patients at Study Entry

Fecal Test	Mean ± SD	Range	Proportion of Patients Exceeding Reference Range Males (n=25)	Females (n=31)	Reference Range[1]
Fecal fat (g/24 hrs)	7.6 ± 8.9	1.0 - 46.0	40	42	0 - 5.0
Fecal bile acids (g/24 hrs)	1.6 ± 1.4	0.2 - 5.3	72	77	0.1 - 0.4
Fecal weight (g/24 hrs)	337 ± 371	51 - 1853	68	48	250

[1] Reference range at the Department of Laboratory Medicine, University of Alberta, 1980.

Table 25: Fecal Data by Site of Crohn's Disease

Fecal Test	Small bowel (n=20)[1] Mean ± SD	Small bowel (n=20)[1] Range	Large bowel (n=4)[1] Mean ± SD	Large bowel (n=4)[1] Range	Small and Large Bowel (n=31)[1] Mean ± SD	Small and Large Bowel (n=31)[1] Range
Fecal fat(g/24 hrs)	9.6 ± 10.8	1.9 - 46.0	3.1 ± 3.0	1.0 - 7.5	6.9 ± 8.0	1.0 - 38.9
Fecal bile acids (g/24 hours)	1.8 ± 1.3	0.2 - 5.3	1.3 ± 1.9	0.2 - 4.1	1.5 ± 1.5	0.2 - 5.3
Fecal weight(g/24 hrs)	398 ± 233	51 - 952	182 ± 81	102 - 258	397 ± 458	59 - 1853

[1] No significant differences were noted among the groups for any parameter

Table 26: Pearson Correlation Coefficients Among Selected Fecal, Urinary, Blood and Clinical Data

Laboratory/Clinical Variable	r value	r^2 value
Fecal weight and fecal fat	0.59**	0.35
Fecal weight and fecal bile acids	0.73**	0.53
Fecal bile acids and fecal fat	0.72**	0.52
Fecal fat and urinary calcium	-0.14	0.02
Fecal bile acids and urinary oxalate	0.44**	0.19
Fecal fat and serum vitamin A	0.07	0.00
Fecal fat and serum carotene	-0.39**	0.15
Fecal fat and prothrombin time	-0.02	0.00
Fecal weight and CDAI[1]	0.11	0.01
Fecal bile acids and CDAI[1]	0.06	0.00
Fecal fat and percent ideal body weight	0.00	0.00
Coefficient of fat absorption[2] and CDAI[1]	-0.23**	0.05
Urinary phosphorus and serum phosphorus	-0.24*	0.06
Urinary calcium and serum calcium	-0.00	0.00

* Correlation coefficient significant ($p<0.05$)

** Correlation coefficient significant ($p<0.01$)

[1] CDAI is the Crohn's Disease Activity Index

[2] Coefficient of fat absorption =

$$\frac{\text{fat intake (g/24 hrs) minus fat output (g/24 hrs)}}{\text{fat intake (g/24 hrs)}} \times 100$$

Table 27: Transformation Data of the Crohn's Disease Activity Index (CDAI) at Entry

Transformation	Mean	SD	SE	Minimum	Maximum	Skewness
Untransformed CDAI	112	97.5	8.3	0	463	1.419
Log CDAI	1.9	0.4	0.0	0.5	2.7	-0.680
Square root CDAI	9.4	4.7	0.4	0.0	21.5	0.138

Table 28: Pearson Correlation Coefficients among Selected Nutrient Intake, Laboratory and Clinical Data

Parameter	r value	r^2 value
Laboratory and Nutrient Intake Correlations		
Serum carotene & vitamin A intake	0.11	0.01
Serum vitamin A & vitamin A intake	0.14*	0.02
Serum vitamin C & vitamin C intake	0.23**	0.05
White cell vitamin C & vitamin C intake	0.11	0.01
Serum folate & folate intake	0.10	0.01
Red cell folate & folate intake	0.13	0.02
Serum B_{12} and B_{12} intake	0.07	0.00
Hemoglobin & iron intake	0.30**	0.09
Hematocrit & iron intake	0.31**	0.10
Serum iron & iron intake	0.13	0.02
Serum ferritin & iron intake	0.05	0.00
Transferrin saturation & iron intake	0.11	0.01
Total iron binding capacity & iron intake	0.08	0.01
Fecal fat & fat intake	0.01	0.00
Fecal weight & dietary fiber intake	-0.08	0.01
CDAI and Nutrient Intake Correlations		
CDAI[1] & energy intake	-0.19*	0.04
CDAI & dietary fiber intake	-0.23**	0.05
CDAI & fat intake	-0.20**	0.04
CDAI & sugar intake	-0.08	0.01
CDAI & sugar intake (as % of calories)	0.11	0.01

Table 28 continued

Pearson Correlation Coefficients among Selected Nutrient Intake, Laboratory and Clinical Data

√CDAI and Laboratory Data Correlations

√CDAI[2]	& hemoglobin	-0.37**	0.14
"	& hematocrit	-0.36**	0.13
"	& serum iron•	-0.24**	0.06
"	& serum ferritin•	-0.06	0.00
"	& transferrin saturation•	-0.22*	0.05
"	& total iron binding capacity	0.06	0.00
"	& white blood cell count	0.04	0.00
"	& total lymphocytes	-0.14	0.02
"	& red blood cell count	-0.23**	0.05
"	& mean red cell volume	-0.15*	0.02
"	& serum albumin	-0.32**	0.10
"	& serum protein	-0.17*	0.03
"	& serum calcium	-0.09	0.01
"	& serum magnesium	-0.09	0.01
"	& serum phosphorus	0.03	0.00
"	& creatinine height index	-0.09	0.01
"	& serum vitamin A	-0.11	0.01
"	& serum carotene•	-0.17	0.03
"	& alkaline phosphatase	0.02	0.00
"	& serum zinc	-0.19*	0.04
"	& serum copper	0.09	0.01
"	& serum folate•	0.04	0.00
"	& red cell folate•	0.22**	0.05
"	& serum B_{12}•	-0.11	0.01
"	& serum vitamin C•	-0.06	0.00
"	& white cell vitamin C•	-0.04	0.00
"	& prothrombin time	0.08	0.01

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* Correlation coefficient significant ($p<0.05$)

** Correlation coefficient significant ($p<0.01$)

• Unsupplemented intakes only

[1] CDAI: Crohn's Disease Activity Index, in the original scale

[2] √CDAI: CDAI transformed to eliminate skewness

Table 29: Principal Factors Analysis: Rank Order of Variables Characterizing General Health in Patients with Crohn's Disease

Factor[1]	Variable	Correlation
1	muscle circumference	.68
	muscle area	.67
	intake-calories	.82
	protein	.81
	fat	.60
	carbohydrate	.79
	phosphorus	.73
	iron	.73
	thiamin	.81
	riboflavin	.64
	niacin	.83
	folate	.69
	sugar	.71
	hemoglobin	.65
	hematocrit	.64
	urinary creatinine	.67
	√CDAI	-.37
2	weight	.66
	% ideal weight	.91
	arm circumference	.87
	% ideal arm circumference	.95
	skinfold	.79
	% ideal skinfold	.71
	fat area	.88
	% ideal fat area	.81
	% ideal muscle circumference	.66
	% ideal muscle area	.67
	basal energy expenditure	.71
	√CDAI	.05
3	red blood cell count	-.63
	serum albumin	-.61
4,6	no correlations >.60	
5	serum iron	.68
	transferrin saturation	.65
7	creatinine height index	.65

[1] Factor 1 consists of those variables which best characterize the general health of patients in this study; in descending order of importance, factors 2 through 7 are also listed

Table 30: Proportion of Counselling and No Counselling Patients taking Nutrient Supplements

Nutrient Supplement	Entry C/NC[1]	3 months C/NC	6 months C/NC
Calcium	18/19	11/21	12/22
Phosphorus	6/7	5/10	5/9
Iron	31/27	28/31	31/28
Vitamin A	33/29	30/33	31/28
Thiamin	39/33	31/36	39/31
Riboflavin	39/33	31/36	39/31
Niacin	39/31	31/34	37/31
Vitamin C	36/34	34/39	39/35
Vitamin B_{12}	33/30	30/33	34/29
Folate	25/19	15/24	17/22

[1] Data presented in 2 columns: counselling(C)/no counselling(NC)

Table 31: Nutrient Intakes of the Counselling and No Counselling Groups at Entry, 3 and 6 Months (Mean ± SD)

Nutrient[1]	Entry		3 Months		6 Months	
	Counselling	No Counselling	Counselling	No Counselling	Counselling	No Counselling
Energy(kcal)	2262±1042	2327±948	2169±899	2430±910	2321±808	2341±897
Protein(g)	81±41	87±35	88±39	89±35	94±34	89±36
Fat(g)	96±51	101±46	93±46	110±51	95±37	98±42
Carbohydrate(g)	262±128	263±122	245±100	266±101	270±110	270±118
Crude Fiber(g)	3.8±2.2	4.1±2.3	4.6±2.7	4.3±2.8	4.7±2.6**	3.6±1.7**
Calcium(mg)	842±743	928±595	894±389	922±500	905±393	943±503
Phosphorus(mg)	1289±711	1387±622	1382±520	1420±625	1450±501	1402±591
Iron(mg)	14.6±7.3	13.9±5.7	14.4±6.8	13.9±5.3	15.5±8.3	13.9±6.2
Vitamin A(IU)	6956±10,365	6390±6155	6257±4963	4962±3211	6568±3776**	4743±3241**
Thiamin(mg)	1.4±0.9	1.2±0.6	1.3±0.7	1.3±0.6	1.3±0.6	1.3±0.6
Riboflavin(mg)	2.2±1.7	2.0±1.2	2.0±0.9	2.1±1.0	2.4±2.0	2.1±1.1
Niacin(mg)	31.3±16.0	32.4±13.6	33.0±15.2	34.0±13.8	36.9±16.3	33.2±13.1
Vitamin C(mg)	150±170	121±109	165±113**	110±82**	184±126**	117±89**
Vitamin B_{12}(μg)	7.2±15.3	5.4±8.4	4.9±5.0	4.2±2.7	5.9±12.7	5.0±6.2
Total Folate (μg)	198±116	184±95	216±102**	178±86**	229±119	193±93

[1] Intake of vitamin or mineral supplements not included

[2] Significant change in mean crude fiber intake ($p<0.01$) at 6 months vs. entry in the counselling group

*,** Within the same time period, means significntly different ($p<0.05$ and $p<0.01$, respectively) for C vs. NC.

Table 32: Range of Nutrient Intakes of the Counselling and No Counselling Groups at Entry, 3 and 6 Months

Nutrient[1]	Entry		3 Months		6 Months	
	Counselling	No Counselling	Counselling	No Counselling	Counselling	No Counselling
Energy (kcal)	576-5756	911-5241	630-5908	918-5422	439-4114	887-4391
Protein (g)	18-204	37-184	29-250	30-172	21-195	26-177
Fat (g)	21-260	35-232	23-299	36-281	10-197	18-197
Carbohydrage (g)	57-664	32-633	53-556	92-544	65-532	89-555
Crude Fiber (g)	0.6-10.4	0.8-10.5	0.3-13.3	0.9-15.2	0.3-12.5	0.4-8.8
Calcium (mg)	72-5750	180-2388	133-1841	216-2325	100-2129	202-2342
Phosphorus (mg)	223-4959	432-3062	419-3024	438-3180	234-2791	340-2906
Iron (mg)	3.7-41.0	4.8-30.0	3.7-35.4	4.8-25.0	4.8-58.8	5.5-35.4
Vitamin A (IU)	537-60,812	763-42,507	925-30,371	1031-17,229	772-16,351	925-22,522
Thiamin (mg)	0.2-4.2	0.2-3.2	0.4-3.7	0.4-3.6	0.2-4.0	0.4-3.1
Riboflavin (mg)	0.2-11.5	0.5-8.0	0.6-4.4	0.6-5.1	0.8-15.5	0.4-4.9
Niacin (mg)	7.1-74.5	11.7-68.9	12.9-88.6	10.8-70.5	10.5-99.9	11.5-62.2
Vitamin C (mg)	1-1212	8-537	3-575	11-346	7-669	8-402
Vitamin B_{12} (µg)	0.5-86.0	0.5-64.0	0.9-35.8	0.5-16.1	0.7-99.9	0.3-42.2
Total Folate (µg)	27-563	42-523	50-527	51-412	39-807	44-491

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[1] Intake of vitamin or mineral supplements not included

Table 33: Proportion of Patients in the Counselling and No Counselling Groups Meeting the Recommended Dietary Allowances (RDA)[1] at Entry, 3 and 6 Months

Nutrient[2]	RDA	Counselling Entry	Counselling 3 Months	Counselling 6 Months	No Counselling Entry	No Counselling 3 Months	No Counselling 6 Months
Energy(kcal)	Full	43	37	53	39	49	40
	2/3	83	86	93	85	90	82
	1/2	86	88	100	91	93	86
	1/3	100	100	100	100	100	100
Protein(g)	Full	79*	93	95*	93	93	88
	2/3	96	100	98	100	100	99
	1/2	99	100	100	100	100	100
	1/3	100	100	100	100	100	100
Calcium(mg)	Full	42	56	56	46	46	54
	2/3	60	82	86	64	73	74
	1/2	82	92	97	83	88	83
	1/3	94	97	98	90	97	95
Phosphorus (mg)	Full	78	89	90	80	84	80
	2/3	93	93	97	96	99	99
	1/2	96	100	98	100	100	99
	1/3	99	100	98	100	100	100
Iron(mg)	Full	52	46	48	49	46	49
	2/3	66	66	71	69	69	68
	1/2	75	84	85	83	85	85
	1/3	96	97	98	94	96	99
Vitamin A (IU)	Full	49	57	66	56	46	48
	2/3	72	75	80	73	72	71
	1/2	79	87	95	86	87	85
	1/3	91	93	98	96	97	95
Thiamin(mg)	Full	58	59	61	47	51	43
	2/3	84	87	90	87	87	85
	1/2	93	93	97	97	99	99
	1/3	96	100	98	99	100	100

Table 33 continued: Proportion of Patients in the Counselling and No Counselling Groups Meeting the Recommended Dietary Allowances (RDA)[1] at Entry, 3 and 6 Months

		Counselling			No Counselling		
Nutrient	RDA	Entry	3 Months	6 Months	Entry	3 Months	6 Months
Riboflavin (mg)	Full	69*	75	88	70	78	75
	2/3	88	93	100	91	94	94
	1/2	97	100	100	97	100	99
	1/3	97	100	100	97	100	99
Niacin (mg)	Full	93	98	97	99	99	99
	2/3	96	100	100	100	100	100
	1/2	100	100	100	100	100	100
	1/3	100	100	100	100	100	100
Vitamin C (mg)	Full	72*	89	90*	71	67	72
	2/3	81	89	95	80	79	82
	1/2	85	90	97	89	84	91
	1/3	91	93	97	94	90	92
Vitamin B_{12}(μg)	Full	57	64	64	64	58	60
	2/3	73	80	85	79	78	80
	1/2	82	90	93	87	90	92
	1/3	90	98	97	94	97	97
Total Folate (μg)		Full	9	5	5	3	33
	2/3	25	31	29	16	15	23
	1/2	45	54	53	34	34	42
	1/3	61	75	83	67	60	69

[1] From Recommended Dietary Allowances, Revised 1980. Food and Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

* Significant increase in the proportion of Counselling patients consuming the full RDA at 6 months vs. entry, for protein, riboflavin and vitamin C

Table 34: Changes in the Proportion of Patients Consuming at Least Two-Thirds of the Recommended Daily Allowance[1,2]

	Counselling(%) Assessment Period		No Counselling(%) Assessment Period	
Nutrient	0-3	0-6	0-3	0-6
Energy - full RDA	-6@	+10@	+10	+1
> 2/3 RDA	-3	+20	+15	-2
Protein - full RDA	+14	+16	0	-5
> 2/3 RDA	+18	+18	0	-6
Calcium - full RDA	+14	+14	0	+8
> 2/3 RDA	+36	+40	+9	+18
Phosphorus - full RDA	+11	+12	+4	0
> 2/3 RDA	+11	+16	+7	+3
Iron - full RDA	-6	-4	-3	0
> 2/3 RDA	-6	+1	-3	-1
Vitamin A - full RDA	+8	+17	-10	-8
> 2/3 RDA	+11	+25	-11	-10
Thiamin - full RDA	+1	+3	+4	-4
> 2/3 RDA	+4	+9	+4	-6
Riboflavin - full RDA	+6	+19	+8	+5
> 2/3 RDA	+11	+31	+5	+8
Niacin - full RDA	+5	+4	0	0
> 2/3 RDA	+9	+8	0	0
Vitamin C - full RDA	+8	+18	-4	+1
> 2/3 RDA	+16	+32	-5	+3
Vitamin B_{12} - full RDA	+7	+7	-6	-4
> 2/3 RDA	+14	+19	-7	-3
Folate - full RDA	-4	-4	0	0
> 2/3 RDA	+2	0	-1	+7

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1 Based on data in Table 33

2 From Recommended Dietary Allowances, Revised 1980. Food & Nutrition Board, National Academy of Sciences, Washington, D.C.

@ Minus or plus signs indicate a decrease or increase, respectively, in the proportion of patients consuming the specified amount of a nutrient

Table 35: Anthropometric Measurements: Mean Percent of Ideal, Standard Deviation and Proportion of Patients Classified as Depleted[1,2] in the Counselling and No Counselling Groups

Anthropometric Parameter	Counselling		No Counselling	
	Mean ± SD	Depleted (%)	Mean ± SD	Depleted (%)
Body weight: Entry	103 ± 20	10	105 ± 17	7
3 months	103 ± 20	10	104 ± 18	7
6 months	103 ± 20	7	104 ± 18	6
Mid-arm circumference:				
Entry	96 ± 14	15	99 ± 12	13
3 months	97 ± 14	11	97 ± 12	15
6 months	98 ± 15	11	98 ± 12	14
Triceps skin-fold:				
Entry	118 ± 58	6	130 ± 54	4
3 months	111 ± 50	3	118 ± 46	7
6 months	109 ± 52	4	121 ± 47	3
Muscle circumference:				
Entry	92 ± 10	20	93 ± 9	17
3 months	94 ± 10	11	94 ± 10	19
6 months	96 ± 10	9	94 ± 9	15

[1] Depletion defined as less than 85% ideal for weight, arm circumference and muscle circumference, and as less than 45% ideal for skin-fold

[2] Ideal arm measurements taken as 50th percentile of Hanes I data, 1977; ideal weight from Metropolitan Life tables, 1959.

Table 36: Hematology and Biochemistry Values of the Counselling and No Counselling Groups at Entry, 3 and 6 Months (Mean ± SD)

Laboratory Test	Entry		3 Months		6 Months	
	Counselling (n=67)	No Counselling (n=70)	Counselling (n=61)	No Counselling (n=67)	Counselling (n=59)	No Counselling (n=65)
Hemoglobin(g/dl)	14.1±1.4	14.1±1.6	14.0±1.5	14.3±1.6	14.2±1.5	14.5±1.4
Hematocrit(%)	41.1±3.4	41.3±4.1	41.5±4.1	42.3±4.6	42.2±4.0	43.1±3.7
Serum iron(µg/dl)	67±34	63±37	73±42	66±38	72±41	73±34
Serum ferritin (ng/ml)	80±84	76±86	66±80	84±113	40±46	56±120
Transferrin saturation (%)	21±11	20±12	23±14	22±13	23±14	24±15
Total iron binding capacity(µg/dl)	328±65	324±59	332±61	317±63	333±61	316±78
White blood cell count (mm^3)	8.3±2.8	8.2±2.6	8.3±2.8	8.4±3.0	8.0±2.5	8.0±3.0
Total lymphocytes(mm^3)	1633±661	1771±859	1940±1134	1782±686	1759±747	1752±884
Red blood cell count (mm^3)	4.6±0.5	4.7±0.5	4.7±0.5	4.8±0.5	4.7±0.5	4.9±0.5
Mean red cell volume (µ^3)	89±6	88±7	89±5	88±6	89±6	89±6
Prothrombin time (%)	99±5	97±5	120±42	98±4	1 case	0 cases
Serum albumin (g/dl)	4.1±0.4	4.1±0.4	4.1±0.4	4.1±0.4	4.2±0.5	4.2±0.4
Serum protein (g/dl)	7.0±0.5	6.9±0.6	6.9±0.5	6.9±0.6	6.9±0.6	6.9±0.6
Serum calcium (mg/dl)	9.3±0.4	9.2±0.4	9.2±0.4	9.2±0.4	9.2±0.3	9.2±0.5
Alkaline phosphatase(IU/l)	88±47	91±30	83±30	87±33	81±23	86±30
Serum magnesium (mg/dl)	2.0-±0.2	1.9±0.2	1.9±0.2	1.9±0.2	1.9±0.1	1.9±0.2
Serum phosphorus (mg/dl)	3.2±0.6	3.4±0.6	3.3±0.5	3.4±0.6	3.4±0.6	3.4±0.5
Serum Vitamin A (µg/dl)	674±204	645±210	711±208	691±226	719±220	705±209

Table 36 continued: Hematology and Biochemistry Values of the Counselling and No Counselling Groups at Entry, 3 and 6 Months (Mean ± SD)

Laboratory Test	Entry		3 Months		6 Months	
	Counselling (n=67)	No Counselling (n=70)	Counselling (n=61)	No Counselling (n=67)	Counselling (n=59)	No Counselling (n=65)
Serum carotene (μg/dl)	85±50	72±31	88±55	75±38	95±61	82±40
Serum zinc (μg/dl)	90±16	86±15	89±20	94±25	103±19	101±13
Serum copper (μg/dl)	141±52	130±34	123±65	138±75	136±44	139±46
Serum folate (ng/ml)	4.3±3.9	4.7±6.9	4.3±3.2	5.8±12.4	5.5±7.3	5.9±9.2
Red cell folate (ng/ml)	688±711	549±357	632±421	594±352	611±614	549±378
Serum B_{12} (pg/ml)	373±193	341±144	366±168	360±153	407±200	354±140
Serum vitamin C (μmol/l)	61±26	65±31	64±25	63±29	65±20	64±26
White cell vitamin C (μmol/10^9)	0.7±0.3	0.7±0.3	0.6±0.2	0.6±0.2	0.8±0.2	0.7±0.2

Table 37: Proportion of Counselling and No Counselling Patients Outside of Reference Range[1,2] at Entry, 3 and 6 Months: Hematological Data

Hematological Test	Counselling Entry (n=67)	Counselling 3 Months (n=61)	Counselling 6 Months (n=51)	No Counselling Entry (n=70)	No Counselling 3 Months (n=67)	No Counselling 6 Months (n=65)
Hemoglobin (g/dl)	5	13	15	8	14	14
Hematocrit (%)	2*	11	13*	8	12	11
Serum iron (μg/dl)	37	45	54	53	49	45
Serum ferritin (ng/ml)[3]						
high	4	4	0	6	6	2
low	17**	62	48**	19**	57	45**
Transferrin saturation(%)	53	49	47	60	45	45
Total iron binding capacity (μg/dl) high	11	11	10	7	14	12
low	11	8	5	10	9	23
White blood cell count ($/mm^3$)	1	5	0	0	0	0
Total lymphocytes ($/mm^3$)	46	33	32	48	37	43
Red blood cell count ($/mm^3$)	23	18	15	16*	16	5*
Mean red cell volume(%)						
high	6	5	7	9	9	8
low	12	15	15	23	18	12
Prothrombin time(%)	0	-	-	0	-	-

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1 Refer to Table 16 for reference range

2 Patients recorded are those with values lower than the stated reference range, except for prothrombin time which records those greater than the reference value. Both extremes are noted for some parameters.

*,** Signifcant difference in the proportion of C or NC who had abnormal values at 6 months vs. entry, $p<0.05$ and $p<0.01$, respectively

Table 38: Proportion of Counselling and No Counselling Patients Outside of Reference Range [1,2] at Entry, 3 and 6 Months: Biochemical Data

Biochemical Test	Counselling Entry (n=67)	Counselling 3 Months (n=61)	Counselling 6 Months (n=51)	No Counselling Entry (n=70)	No Counselling 3 Months (n=67)	No Counselling 6 Months (n=65)
Serum albumin (g/dl)	0	0	0	0	1	0
Serum protein (g/dl)	1	2	3	1	3	6
Creatinine height index (%)	32	-	-	41	-	-
Serum calcium (mg/dl)	0	0	0	0	0	0
Alkaline phosphatase(IU/1)	16	19	7	21	20	18
Serum magnesium (mg/dl)[3]	3	-	2	1*	-	11*
Serum phosphorus (mg/dl)	9	5	5	1	6	3
Serum vitamin A (µg/dl)[3]	0	0	0	0	0	0
Serum carotene (µg/dl)	22	26	23	19	23	17
Serum zinc (µg/dl)	1	-	0	1	-	0
Serum copper (µg/dl)	1	-	5	3	-	0
Serum folate (ng/ml)	10	7	7	10	7	5
Red cell folate (ng/ml)[3]	9	5	16	10	9	10
Serum B_{12} (pg/ml)[3]	4	10	9	3	2	3
Serum vitamin C (µmol/l)	17	8	7	13	15	11
White cell vitamin C (µmol/10^9)[3]	37	63	24	37	59	46

[1] Refer to Table 17 for reference range

[2] Patients recorded are those with values lower than the stated refernce range, except for alkaline phosphatase which records those greater than the reference range

[3] Serum vitamin A, red cell folate, and serum B_{12} at 3 months, white cell vitamin C at 3 months and 6 months, and serum magnesium at 6 months were assessed on selected (i.e. sicker) patients only.

* Significant difference in the proportion of NC who had an abnormal serum magnesium value at 6 months vs. entry ($p<0.05$)

Table 39: Laboratory Data: Changes in the Proportion of Patients Outside of Reference Range[1]

Laboratory Parameter		Counselling 0-3	Counselling 0-6	No Counselling 0-3	No Counselling 0-6
Hemoglobin		+8@	+10	+6	+7
Hematocrit		+10	+12	+5	0
Serum iron		+8	+17	-8	-9
Serum ferritin	high	-	0	-	0
	low	-	+32	-	+26
Transferrin saturation		0	-6@	-15	-15
Total iron binding capacity	high	0	0	+7	+5
	low	0	-6	0	+13
White blood cell count		0	0	0	0
Total lymphocytes		-13	-14	-11	-5
Red blood cell count		0	-8	0	-11
Mean red cell volume	high	0	0	0	0
	low	0	0	-5	-11
Prothrombin time		-	-	-	-
Serum albumin		0	0	0	0
Serum protein		0	0	0	+5
Serum calcium		0	0	0	0
Alkaline phosphatase		0	-9	0	0
Serum magnesium		-	0	-	+10
Serum phosphorus		0	0	+5	0
Serum vitamin A		0	0	0	0
Serum carotene		0	0	0	0
Serum zinc		-	0	-	0
Serum copper		-	0	-	0
Serum folate		0	0	0	-5
Red cell folate		0	+7	0	0
Serum B_{12}		+6	+5	0	0
Serum vitamin C		-9	-10	0	0
White cell vitamin C		+26	-13	+22	+9

[1] Only changes of ±5% or greater are indicated; smaller changes denoted by 0; dashes denote time periods when too few patients were assessed to give a valid comparison

@ Plus or minus signs indicate an increase or decrease, respectively, in the proportion of patients outside the reference range

Table 40: Proportion of Patients Changing from Low to Normal or Normal to Low Laboratory Values for Selected Parameters

	Entry to 3 Months		Entry to 6 Months	
Laboratory Parameter	Low to Normal[1] C/NC[2]	Normal to Low C/NC	Low to Normal C/NC	Normal to Low C/NC
Serum iron	36/34	24/28	29/39	25/32
Serum ferritin	30/64**	23/20	40/58	31/35
Total iron binding capacity	60/67	6/7	50/29*	2/19**
Total lymphocytes	43/43	22/18	52/47	22/32
Serum folate	17/40**	2/5	50/0**	6/4
Red blood cell folate	60/100**	0/12**	40/67**	13/8
Serum vitamin C	56/25**	5/10	63/38*	3/4
White blood cell vitamin C	25/50**	45/67*	67/40**	7/38**
Serum carotene	25/38	45/38	15/13	16/6

1 "Normal" and "Low" refer to laboratory values within and below the reference range, respectively

2 Data presented in 2 columns: counselling/no counselling

*,** Proportions of C and of NC significantly different at the 5% and 1% level of probability, respectively

Table 41: Mean squares from the Analysis of Covariance for the Square Root Transformed Crohn's Disease Activity Index (√CDAI)

Source of Variation	d.f.[1]	0-3 months	3-6 months	0-6 months
Covariates				
Initial √CDAI value	1	1217.3**	1045.6**	768.7**
Age	1	7.8	0.5	7.3
Season of entry	1	1.5	2.5	1.5
Duration of disease	1	14.0	15.7	51.7+
Main Effects				
Counselling(C)	1	73.0*	3.7	68.4*
Sex(S)	1	0.0	29.6	44.7+
Small Bowel Surgery(B)	1	4.0	37.4+	35.0
Interactions				
C X S	1	1.4	0.0	0.6
C X B	1	71.4*	10.6	2.4
S X B	1	1.5	22.5	12.8
Error	92	12.6	13.3	15.5

1 Degrees of freedom

+,*,** Mean squares were significant at the 10%, 5% and 1% level of probability, respectively

Table 42: Covariance Adjusted Means and Newman-Keul Range Tests for the Square Root Transformed Crohn's Disease Activity Index (√CDAI)

Category	N	0-3 months	3-6 months	0-6 months
Counselling	49	8.2(67)Δb@	8.9(80)a	8.3(68)b
No Counselling	54	9.9(98)a	9.4(87)a	10.0(100)a
Male	47	9.0(81)a	9.8(95)a	9.9(98)z
Female	56	9.2(85)a	8.7(75)a	8.5(73)y
Small Bowel Surgery	46	9.3(87)a	9.9(98)z	9.9(97)a
No Small Bowel Surgery	57	8.9(79)a	8.6(74)y	8.6(74)a

Δ Number in the brackets is the value of the adjusted mean in the original scale, i.e. $(\sqrt{CDAI})^2$

@ Adjusted means followed by different letters a or b, y or z within the same main effect and column are significantly different at the 5% and 10% level of probability, respectively

Table 43: Proportion of Patients in the Counselling and No Counselling Groups in which Crohn's Disease Activity Changes from Active to Inactive, and From Inactive to Active[1]

	Active to Inactive	Inactive to Active
Entry to 3 months:		
Counselling	16%	11%
No Counselling	9%	15%
Entry to 6 months:		
Counselling	22%*	12%
No Counselling	8%*	18%

[1] Active disease defined as CDAI greater than 150; inactive disease as CDAI less than or equal to 150.

* Proportion of patients in which Crohn's disease activity changed from active to inactive was significantly higher in C vs. NC, $p<0.05$

Table 44: Mean Modified Crohn's Disease Activity Index and Oxford Scores of the Counselling and No Counselling Groups

Index	Study Period	Counselling	No Counselling
Modified CDAI[1]	Entry	3.9	2.9
	3 months	3.4	3.3
	6 months	3.2	3.5
Oxford[1]:	Entry	1.8	1.5
	3 months	1.6	1.5
	6 months	1.4	1.6

[1] Net change in index score from entry to 6 months significant in counselling group for the modified CDAI ($p<0.05$) and for the Oxford score ($p<0.01$)

Table 45: Surgery and Hospital Admissions Data of the Counselling and No Counselling Groups

Assessment Period		Counselling	No Counselling
3 months:	patients having surgery since entry	5(8%)	5(7%)
	patients entering hospital since entry	9(15%)	11(16%)
	total days in hospital since entry	137	117
	mean days in hospital:		
	all patients/only admitted patients	2.2/15.2	2.3/10.6
6 months:	patients having surgery since 3 months	3(5%)	2(3%)
	patients entering hospital since 3 months	5(8%)	5(8%)
	total days in hospital since 3 months	18**	99**
	mean days in hospital since 3 months:		
	all patients/only admitted patients	0.4/3.6	1.5/19.8
Total at 6 months:	patients having surgery since entry	8(13%)	7(11%)
	patients entering hospital since entry	14(23%)	16(25%)
	total days in hospital since entry	155*	216*
	mean days in hospital:		
	all patients/only admitted patients	2.6/11.1	3.3/13.5

*,** Significant difference in total days for counselling vs. no counselling, $p<0.05$ and $p<0.01$, respectively

Table 46: Days of Work Missed due to Crohn's Disease for Counselling and No Counselling Groups[1]

Assessment Period		Counselling	No Counselling
3 months:	patients missing work since entry	12(20%)	15(22%)
	total days of work missed since entry	183	192
	mean work days missed:		
	all patients/only those missing work	3.3/15.3	3.0/12.8
6 months:	patients missing work since 3 months	11(19%)	15(23%)
	total days of work missed since 3 months	114**	334**
	mean work days missed since 3 months:		
	all patients/only those missing work	2.1/10.4	5.3/22.3
Total at 6 months:	patients missing work since entry	23(38%)	30(46%)
	total days of work missed since entry	297**	526**
	mean work days missed since entry:		
	all patients/only those missing work	5.0/12.9	8.1/17.5

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[1] Data collected from patients with full time employment and those attending an academic institution; data from housewives excluded

** Significant difference in total days for counselling vs. no counselling, $p < 0.01$

Table 47: Proportion of Patients Taking Prednisone or Salazopyrin®, and Dose of Medication, in the Counselling and No Counselling Groups

Medication		Counselling % taking medication	Counselling Dose(mg/day)^{1,2}	No Counselling % taking medication	No Counselling Dose(mg/day)$^{1.2}$
Prednisone:	Entry	48	7.0/14.9	36	5.5/14.7
	3 months	39	6.0/14.8	35	6.5/18.0
	6 months	37	6.5/16.8	39	6.5/16.7
Salazopyrin®:	Entry	42	1.3/5.9	53	1.6/5.8
	3 months	36	1.1/6.0	47	1.6/6.8
	6 months	32	1.1/6.4	50	1.6/6.3

1 Data on dose of medication presented in 2 columns: mean dose of group as a whole/mean dose of only those patients taking Prednisone or Salazopyrin®

2 Prednisone dose in mg/day, Salazopyrin® dose in g/day

Table 48: Proportion of Patients Stopping or Decreasing Dose of Prednisone or Salazopyrin®, and Size of Dose Decrease, in the Counselling and No Counselling Groups

Medication		Counselling			No Counselling		
		Stopped (%)	Decreased (%)	Size of Decrease[1]	Stopped (%)	Decreased (%)	Size of Decrease[1]
Prednisone:	Entry to 3 months	29	20	11.0	26	12	11.5
	Entry to 6 months	36	20	11.5	12	11	11.0
Salazopyrin:	Entry to 3 months	9	8	2.2	6	3	0.8
	Entry to 6 months	26[2]	14	2.5	3[2]	5	1.4

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[1] Prednisone dose in mg/day; Salazopyrin® dose in g/day

[2] Proportion of counselling patients able to stop taking Salazopyrin® was significantly greater than proportion of no counselling patients, $p<0.05$

Table 49: Proportion of Patients Starting or Increasing Dose of Prednisone or Salazopyrin®, and Size of Dose Increase in the Counselling and No Counselling Groups

Medication		Counselling			No Counselling		
		Started (%)	Increased (%)	Size of Increase[1]	Started (%)	Increased (%)	Size of Increase[1]
Prednisone:	Entry to 3 months	3	10	10.5	8	11	23.5
	Entry to 6 months	5	14	17.5	8	12	20.5
Salazopyrin®:	Entry to 3 months	2	3	2.5	0	5	1.9
	Entry to 6 months	3	7	3.0	3	8	1.9

[1] Prednisone dose in mg/day; Salazopyrin® dose in g/day

Table 50: Characteristics of Ensure® Study Groups at Randomization

Characteristic	Counselling		No Counselling	
	Ensure®(M11,F17) Mean ± SD	No Ensure®(M15,F17) Mean ± SD	Ensure®(M16,F18) Mean ± SD	No Ensure®(M16,F15) Mean ± SD
Age at September 1/81(yrs)	34.0±11.9	36.4±10.3*	34.2±10.5	29.2±7.9*
Duration of disease(yrs)	6.5±4.2	6.0±3.6	7.1±4.2	6.9±6.2
Crohn's Disease Activity Index	114±102	85±77	129±104	92±80
Length of small bowel resected(inches)	7.4±13.5	15.4±24.1	6.1±11.6	9.4±14.1
% ideal body weight	99±16	108±24	102±21	105±16
% taking Prednisone	29	44	44	35
% taking Salazopyrin®	36	31	56	45

* Mean age of counselling no Ensure® group significantly greater than that of the no counselling no Ensure® group, $p<0.05$ different within the same patient characteristic, $p<0.05$

Table 51: Effects of Counselling Upon Ensure® Compliance

Percent of Prescribed Cans of Ensure® Consumed		Mean ± SD
9 months	counselling	41 ± 37
	no counselling	32 ± 24
12 months	counselling	36 ± 39
	no counselling	15 ± 18
Cans of Ensure® Consumed Per Day		
9 months	counselling	0.7 ± 0.9
	no counselling	0.4 ± 0.6
12 months	counselling	0.7 ± 0.9
	no counselling	0.2 ± 0.3
Proportion of Patients Who Stopped Taking Ensure®		Proportion
9 months	counselling	35
	no counselling	31
12 months	counselling	46
	no counselling	64

Table 52: Proportion of Patients in the Compliant and Non-Compliant Ensure® Groups Experiencing Problems with Ensure® Consumption

Problem Encountered	Total Patients(%) 9 mo/12 mo n=57/n=53	Compliant Ensure®(%) 9 mo/12 mo n=15/n=7	Non-Compliant Ensure®(%) 9 mo/12 mo n=42/n=46
Dislike Flavor	53/26	13/0	40/26
Bloating	51/30	20/0	31/30
Decreases Appetite	37/22	20/0	17/22
Diarrhea	30/31	13/14	17/17
Gas	28/13	7/0	21/13
Coats Tongue/Teeth	24/17	0/0	24/17
Abdominal Pain	21/11	7/0	14/11
Other^2	21/35	0/0	21/35

[1] Compliant defined as those patients taking the prescribed amount of Ensure®; non-compliant defined as those patients not taking the prescribed amount of Ensure®

[2] Other problems include weight gain, didn't want to bother, miscellaneous

Table 53: Effects of Counselling-Ensure® Randomization on Nutrient Intake[1]: Proportion of Patients Consuming the Full Recommended Dietary Allowance[2]

		Counselling		No Counselling	
		Ensure®	No Ensure®	Ensure®	No Ensure®
Nutrient	Month:	6/9/12	6/9/12	6/9/12	6/9/12
Energy		56/48/54	52/33/55	46/49/42	36/47/46
Protein		100/96/88	91/87/93	91/100/97	84/83/83
Calcium		63/42/54	50/63/41	61/57/46	45/33/35
Phosphorus		96/83/83	84/87/87	85/83/82	74/73/79
Iron		48/42/42	47/53/48	42/51/46	58/50/41
Vitamin A		82/63/54	53/50/72	55/43/49	42/33/48
Thiamin		70/63/75	53/67/72	52/66/49	36/50/48
Riboflavin		93/88/75	84/77/76	76/86/76	74/53/55
Niacin		100/96/92	94/93/100	97/100/97	100/100/93
Vitamin C		89/79/75	91/87/90	76/69/58	68/80/76
Vitamin B_{12}		67/79/75	63/67/66	61/71/64	58/37/52
Folate		7/8/4	3/10/0	0/3/0	7/0/3

[1] Intake from food and Ensure® combined for months 9 and 12; from food alone for month 6

[2] From Recommended Dietary Allowances, Revised 1980. Food and Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

Table 54: Effects of Ensure® Compliance on Nutrient Intake[1]: Proportion of Patients Consuming the Full Recommended Dietary Allowance[2]

	No Ensure®[3]	Ensure®-Compliant[3]	Ensure®-Stopped[3]
Nutrient Month:	6/9/12	6/9/12	6/9/12
Energy	44/39/50	53/53/52	50/39/45
Protein	87/85/86	97/100/96	89/95/94
Calcium	48/49/37	61/53/64	61/42/39
Phosphorus	79/80/81	92/87/88	83/74/81
Iron	52/53/46	45/53/52	44/37/36
Vitamin A	48/41/59	63/61/44	67*/32*/58
Thiamin	44/59/59	66/74/64	44/42/58
Riboflavin	79/66/64	84/92/88	78/74/68
Niacin	97/97/95	97/100/96	100/95/97
Vitamin C	79/84/83	76/76/76	89*/63/55*
Vitamin B_{12}	60/53/58	63*/87*/84	61/47/58
Folate	5/5/2	5/3/4	0/11/0

[1] Intake from food and Ensure® combined for months 9 and 12; from food alone for month 6

[2] From Recommended Dietary Allowances, Revised 1980. Food and Nutrition Board, National Research Council, National Academy of Sciences, Washington, D.C.

[3] No Ensure® group includes patients not randomized to the Ensure® group; Ensure®-compliant group includes patients randomized to the Ensure® group and who did not stop taking Ensure®; Ensure®-stopped group includes patients randomized to the Ensure® group but who stopped consuming it at some point in time

* Significant change in the proportion of patients consuming the full RDA, $p<0.05$

Table 55: Mean Percent Ideal Body Weight[1] of Counselling-Ensure® and Ensure® Compliance Groups

Counselling-Ensure® Randomization	6 months[2]	9 months	12 months
Counselling: Ensure®	108±24[3]	107±26	107±25
No Ensure®	99±16	99±18	100±19
No Counselling: Ensure®	105±16	105±16	107±16
No Ensure®	102±21	102±18	101±19
Ensure® Compliance Group[4]			
No Ensure®	101±19	101±18	101±19
Ensure®-Compliant	107±18	107±19	106±21
Ensure®-Stopped	106±23	104±24	108±20

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[1] Standard from Metropolitan Life, 1959

[2] No Ensure® had yet been consumed at the 6 month assessment; these data provide a standard of comparison

[3] Mean ± SD

[4] No Ensure® group includes patients not randomized to the Ensure® group Ensure®-compliant group includes patients randomized to the Ensure® group and who did not stop taking Ensure®; Ensure®-stopped group includes patients randomized to the Ensure® group but who stopped consuming it at some point in time

Table 56: Selected Laboratory Data of Counselling-Ensure® Groups

Laboratory Test[1]	Assessment Period	Counselling		No Counselling	
		Ensure®	No Ensure®	Ensure®	No Ensure®
Hemoglobin(g/dl)	6 mo.[2]	14.1±1.7[3]	14.3±1.4	14.8±1.3	14.1±1.4
	9 mo.	14.6±1.1	14.1±1.4	14.8±1.5	14.1±1.3
	12 mo.	14.1±1.7	14.3±1.2	14.7±1.4	14.3±1.4
Hematocrit(%)	6 mo.	42±4	42±4	44±4	42±3
	9 mo.	43±3	42±4	42±3	42±4
	12 mo.	42±5	42±3	44±4	42±4
Transferrin saturation(%)	6 mo.	22±13	23±16	28±16	20±12
	9 mo.	22±13	26±15	28±16	22±14
	12 mo.	24±14	23±12	21±10	22±16
Total lymphocyte count($/mm^3$)	6 mo.	1867±691	1668±790	1704±969	1815±809*
	9 mo.	1657±575	1569±726	1759±1310	1786±820
	12 mo.	1656±726	1959±921	1658±719	1517±615*
Serum albumin (g/dl)	6 mo.	4.2±0.3	4.2±0.6	4.2±0.4	4.1±0.4
	9 mo.	4.2±0.4	4.1±0.5	4.2±0.3	4.1 ±0.3
	12 mo.	4.2±0.4	4.2±0.5	4.3±0.3	4.1±0.3
Serum folate (ng/ml)	6 mo.	7.3±10.4	4.0±2.2	4.1±3.0	5.9±7.4
	9 mo.	6.7±10.1	7.6±17.6	4.3±2.8	7.5±12.5
	12 mo.	7.1±10.8	5.5±5.8	6.5±11.3	7.5±11.3
Serum vitamin C (μmol/l)	6 mo.	63±24	67±16	66±26	61±27
	9 mo.	68±30	63±25	74±28	73±33
	12 mo.	67±29	64±22	63±21	74±34

Table 56 continued: Selected Laboratory Data of Counselling-Ensure® Groups

		Counselling		No Counselling	
Laboratory Test	Assessment Period	Ensure®	No Ensure®	Ensure®	No Ensure®
Serum vitamin B_{12}(pg/ml)	6 mo.	406±218	407±186*	343±111*	367±169*
	9 mo.	364±112	382±269	327±115	275±154
	12 mo.	336±213	312±209*	281±139*	280±158*
Serum carotene (μg/dl)	6 mo.	100±73	91±50	89±45	78±32
	9 mo.	93±66	81±46	82±34	74±42
	12 mo.	93±75	85±52	83±31	78±37

1 For reference ranges, see Tables 16 and 17
2 No Ensure® had yet been consumed at the 6 month assessment; these data provide a standard of comparison
3 Mean ± SD
* Significant difference in mean laboratory value at 6 months vs. 12 months withn the same Counselling-Ensure® group, $p<0.05$

Table 57: Selected Laboratory Data of Ensure® Compliance Groups^{1}

Laboratory Test^{2}	Assessment Period	No Ensure®	Ensure®-Compliant	Ensure®-Stopped
Hemoglobin(g/dl)	6 mo.^{3}	14.2±1.4^{4}	14.4±1.8	14.8±1.2
	9 mo.	14.1±1.3	14.7±1.4	14.7±1.2
	12 mo.	14.3±1.3	14.4±1.8	14.5±1.4
Hematocrit(%)	6 mo.	42±4	43±5	44±3
	9 mo.	42±4	43±4	43±3
	12 mo.	42±3	43±5	43±4
Transferrin saturation(%)	6 mo.	21±14	25±15	25±14
	9 mo.	24±15	26±16	22±13
	12 mo.	23±14	23±12	21±12
Total lymphocyte count(/mm^{3})	6 mo.	1741±796	1779±966	1761±680
	9 mo.	1677±776	1687±1271	1751±489
	12 mo.	1738±808	1534±672	1756±744
Serum albumin(g/dl)	6 mo.	4.2±0.5	4.2±0.3	4.3±0.4
	9 mo.	4.1±0.4	4.2±0.4	4.2±0.4
	12 mo.	4.1±0.4	4.3±0.3	4.2±0.4
Serum folate(ng/ml)	6 mo.	4.9±5.4	5.9±8.9	5.0±3.5
	9 mo.	7.5±15.1	5.7±8.3	4.4±2.6
	12 mo.	6.5±9.0	6.2±10.0	7.2±11.8
Serum vitamin C (μmol/l)	[illegible] mo.	64±22	67±24	60±29
	9 mo.	68±30	71±28	72±32
	12 mo.	69±29	69±26	62±23

Table 57 continued: Selected Laboratory Data of Ensure® Compliance Groups

Laboratory Test[2]	Assessment Period	No Ensure®	Ensure®-compliant	Ensure®-stopped
Serum vitamin B_{12}(pg/ml)	6 mo.	388±178**	336±137	440±198**
	9 mo.	329±221	345±110	344±145
	12 mo.	296±185**	330±211	282±136**
Serum carotene(μg/dl)	6 mo.	84±42	95±65	92±53
	9 mo.	78±44	91±54	78±40
	12 mo.	82±45	83±42	91±62

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[1] No Ensure® group includes patients not randomized to the Ensure® group; Ensure®-compliant group includes patients randomized to the Ensure® group and who did not stop taking Ensure®; Ensure®-stopped group includes patients randomized to the Ensure® group but who stopped consuming it at some point in time

[2] For reference ranges, see Tables 16 and 17

[3] No Ensure® had yet been consumed at the 6 month assessment; these data provide a standard of comparison

[4] Mean ± SD

** Significant difference between mean serum vitamin B_{12} level at 6 months vs. 12 months within the No Ensure® group and within the Ensure®-stopped group ($p<0.01$)

Table 58: Mean Squares from the Analysis of Covariance for the Square Root Transformed Crohn's Disease Activity Index (√CDAI) for the Ensure® Experiment

Source of Variation	d.f.	6-9 months	9-12 months	6-12 months
Covariates				
Initial √CDAI	1	652.9**	1066.2**	930.9**
Age	1	0.0	44.6^{+}	61.5*
Season of Entry	1	21.2	21.8	0.2
Duration of disease	1	20.2	7.7	1.6
Main Effects				
Counselling (C)	1	22.6	5.4	0.1
Ensure® (E)	1	32.0^{+}	8.8	22.8
Sex (S)	1	6.6	17.8	49.2^{+}
Small Bowel Surgery (B)	1	16.2	3.7	5.8
Interactions				
C X E	1	17.6	19.3	0.0
C X S	1	6.4	8.6	14.1
C X B	1	43.3*	8.8	38.2^{+}
E X S	1	13.6	8.8	21.3
E X B	1	3.1	6.5	1.1
S X B	1	18.8	17.9	0.5
Error	86	10.7	12.4	13.4

$^{+}$, *, ** Mean squares were significant at the 10%, 5% and 1% level of probability, respectively

Table 59: Covariance Adjusted Means and Newman-Keul Range Tests for the Square Root Transformed Crohn's Disease Activity Index (√CDAI) for the Ensure® Experiment

Category	N	6-9 months	9-12 months	6-12 months
Counselling	47	7.4(55)Δa	8.5(72)a	8.2(67)a
No Counselling	54	8.3(69)a	8.1(66)a	8.3(69)a
Ensure®	50	7.3(53)z@	8.0(64)a	7.7(59)a
No Ensure®	51	8.5(72)y	8.6(74)a	8.9(79)a
Male	45	7.6(58)a	7.8(61)a	7.4(55)z
Female	56	8.1(66)a	8.7(76)a	8.9(79)y
Small Bowel Surgery	46	8.4(71)a	8.5(72)a	8.6(74)a
No Small Bowel Surgery	55	7.5(56)a	8.1(66)a	8.0(64)a

Δ Number in brackets is the value of the adjusted mean in the original scale

@ Adjusted means followed by different letters within the same main effect and column are significantly different at the 10% level of probability

Table 60: Mean Squares from the Analysis of Covariance for the Square Root Transformed Crohn's Disease Activity Index (√CDAI) for the Ensure® Experiment, Accounting for Compliance to Ensure®

Source of Variation	d.f.	6-9 months	9-12 months	6-12 months
Covariates				
Inital √CDAI	1	659.1**	1058.9**	940.4**
Age	1	0.4	43.9$^+$	57.1*
Season of Entry	1	25.4	21.5	0.0
Duration of disease	1	16.4	7.9	0.7
Main Effects				
Ensure® Compliance Group (E)	4	26.4$^+$	13.2	7.8
Sex (S)	1	10.4	18.1	57.5*
Small Bowel Surgery (B)	1	9.1	2.9	2.1
Interactions				
E X S	4	4.9	7.8	14.0
E X B	4	16.3	7.4	17.5
S X B	1	25.9	16.1	0.0
Error	80	10.7	12.8	13.6

$^+$, *, ** Mean squares were significant at the 10%, 5% and 1% level of probability, respectively

Table 61: Covariance Adjusted Means and Newman-Keul Range Tests for the Square Root Transformed Crohn's Disease Activity Index ($\sqrt{CDAI}$) for the Ensure® Experiment, Accounting for Compliance to Ensure®

Category	N	6-9 months	9-12 months	6-12 months
Counselling - No Ensure®	25	8.5(72)[Δ]z@	8.4(71)a	8.9(79)a
Counselling - Compliant[1]	5	8.3(69)yz	6.8(46)a	7.3(53)a
Counselling - Not Compliant	17	5.6(31)y	9.3(86)a	7.6(58)a
No Counselling - No Ensure®	26	8.5(72)yz	8.7(76)a	8.7(76)a
No Counselling - Not Compliant	27	8.1(66)yz	7.3(53)a	7.7(59)a
Male	44	7.5(56)a	7.7(59)a	7.3(53)b
Female	56	8.2(67)a	8.6(74)a	9.0(81)a
Small Bowel Surgery	45	8.2(67)a	8.5(72)a	8.4(71)a
No Small Bowel Surgery	55	7.6(58)a	8.1(66)a	8.1(66)a

Δ Number in brackets is the value of the adjusted mean in the original scale

@ Adjusted means followed by different letters [(a-b),(y-z)] within the same main effect and column are significantly different at the 5% and 10% level of probability, respectively

[1] Compliant defined as taking at least 50% of prescribed cans of Ensure®

Table 62: Covariance Adjusted Means and Newman-Keul Range Tests for the Square Root Transformed Crohn's Disease Activity Index ($\sqrt{CDAI}$) for Ensure® Compliance Groupings

	33% Compliance[1]			
Category	N	6-9 months	9-12 months	6-12 months
Counselling-No Ensure®	25	8.4(71)[Δ]yz[@]	8.5(72)a	8.9(79)a
Counselling - Compliant	6	7.9(62)yz	6.8(46)a	6.9(48)a
Counselling - Not Compliant	16	5.6(31)z	9.4(88)a	7.7(59)a
No Counselling - No Ensure®	26	8.4(71)yz	8.7(76)a	8.6(74)a
No Counselling - Compliant	4	6.0(36)yz	5.9(35)a	5.3(28)a
No Counselling - Not Compliant	24	8.6(74)y	7.7(59)a	8.4(71)a
	25% Compliance[1]			
Counselling - No Ensure®	25	8.4(71)yz	8.5(72)a	7.9(62)a
Counselling - Compliant	8	7.4(55)yz	7.7(59)a	7.8(61)a
Counselling - Not Compliant	14	5.6(31)z	9.3(86)a	7.4(55)a
No Counselling - No Ensure®	26	8.4(71)yz	8.7(76)a	8.6(74)a
No Counselling - Compliant	7	6.4(41)yz	6.4(41)a	6.0(36)a
No Counselling - Not Compliant	21	8.8(77)y	7.8(61)a	8.6(74)a

Δ Number in brackets is the value of the adjusted mean in the original scale

@ Adjusted means followed by different letters within the same column are significantly different at the 10% level of probability

[1] 33% and 25% compliance defined as taking at least 33% or 25% of prescribed cans of Ensure®

Table 63: Proportion of Patients Taking Prednisone or Salazopyrin® in the Counselling-Ensure® Groups

	Counselling		No Counselling	
	Ensure®	No Ensure®	Ensure®	No Ensure®
Prednisone				
6 months	29	44	44	35
9 months	25	47	44	39
12 months	25	44	41	35
Salazopyrin®				
6 months	36	31	56	45
9 months	25	28	56	35
12 months	21	25	50	29

Table 64: Porportion of Patients Taking Prednisone or Salazopyrin® in the Ensure®-Compliance Groups

	No Ensure®	Ensure®-Compliant	Ensure®-Stopped
Prednisone			
6 months	40	37	42
9 months	43	37	42
12 months	40	28	45
Salazopyrin®			
6 months	38	42	53
9 months	32	39	53
12 months	27	28	52

Table 65: Surgery, Hospital Admissions and Work Missed by Counselling-Ensure® Groups

Assessment Period	Counselling Ensure®	Counselling No Ensure®	No Counselling Ensure®	No Counselling No Ensure®
9 months:	n=24	n=31	n=35	n=30
patients having surgery since 6 months	0%	4%	0%*	13%*
patients entering hospital since 6 months	0%	6%	6%	13%
total days in hospital since 6 months	0**	35**	12**	111**
mean days in hospital: all patients/only admitted patients	0.0/0.0	1.1/17.5	0.3/6.0	3.7/27.8
patients missing work since 6 months	17%	13%	12%	10%
total days of work missed since 6 months	11	6	116*	85*
mean work days missed: all patients/only those missing work	0.5/2.8	1.2/1.5	4.0/29.0	2.0/28.3
12 months:	n=24	n=30	n=33	n=29
patients having surgery since 9 months	0%	7%	0%	0%
patients entering hospital since 9 months	9%	13%	3%	10%
total days in hospital since 9 months	33**	126**	33**	16**
mean days in hospital: all patients/only admitted patients	1.4/16.5	4.2/31.5	1.0/33.0	0.6/5.3
patients missing work since 9 months	17%	13%	18%	17%
total days of work missed since 9 months	27**	133**	138**	18**
mean work days missed: all patients/only those missing work	1.3/6.8	5.1/33.3	4.2/23.0	0.6/3.6
Total at 12 months:				
patients having surgery since 6 months	0%	11%	0%[1]	13%[1]
patients entering hospital since 6 months	9%	19%	9%	23%
total days in hospital since 6 months	33**	161**	45**	127**
mean days in hospital: all patients/only admitted patients	1.4/16.5	5.4/26.8	1.4/15.0	4.4/18.1
patients missing work since 6 months	34%	26%	30%	27%
total work days missed since 6 months	38**	139**	254**	103**
mean work days missed: all patients/only those missing work	1.6/4.8	4.6/17.4	7.7/25.4	3.6/12.9

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[1] Significant difference in the proportion of patients having surgery in no counselling plus Ensure® vs. no counselling, no Ensure®, ($p<0.05$)

*,** Significant difference in total days for Ensure® vs. no Ensure® within the counselling or no counselling groups, $p<0.05$ and $p<0.01$, respectively

Table 66: Surgery, Hospital Admissions and Work Missed by Ensure® Compliance Groups

Assessment Period	No Ensure®[1]	Ensure® Compliant[1]	Ensure®-stopped[1]
9 months:	n=62	n=38	n=19
patients having surgery since 6 months	8%	0%	0%
patients entering hospital since 6 months	10%	5%	0%
total days in hospital since 6 months	146a	12b	0c
mean days in hospital: all patients/only admitted patients	2.4/24.3	0.3/6.0	0.0/0.0
patients missing work since 6 months	11%	11%	21%
total days of work missed since 6 months	91a	17b	107a
mean work days missed: all patients/only those missing work	1.5/13.0	0.4/4.3	5.6/26.8
	n=60	n=24	n=31
12 months:			
patients having surgery since 9 months	3%	0%	0%
patients entering hospital since 9 months	12%	13%	0%
total days in hospital since 9 months	142a	66b	0c
mean days in hospital: all patients/only admitted patients	2.4/20.3	2.8/22.0	0.0/0.0
patients missing work since 9 months	15%	25%	13%
total days of work missed since 9 months	92a	76a	89a
mean work days missed: all patients/only those missing work	1.5/10.2	3.2/12.7	2.9/22.3
Total at 12 months:			
patients having surgery since 6 months	11%	0%	0%
patients entering hospital since 6 months	22%[2]	18%	0%[2]
total days in hospital since 6 months	288a	78b	0c
mean days in hospital: all patiens/only admitted patients	4.8/22.2	3.3/19.5	0.0/0.0
patients missing work since 6 months	26%	36%	34%
total work days missed since 6 months	183a	93b	196a
mean work days missed: all patients/only those missing work	3.1/11.4	3.9/10.3	10.3/32.7

---

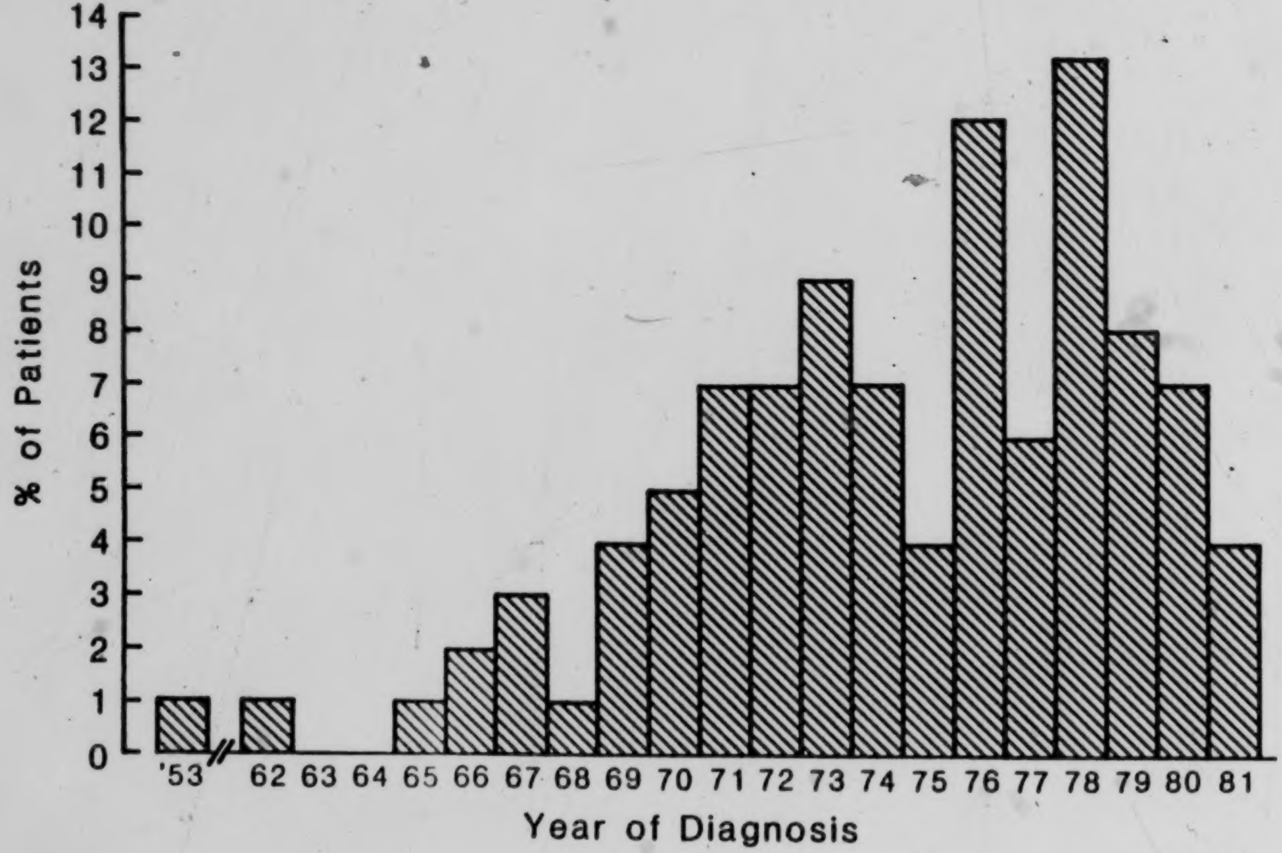
1 No Ensure® group includes patients not randomized to Ensure®; Ensure®-compliant group includes patients randomized to Ensure® who did not stop taking Ensure®; Ensure®-stopped group includes patients randomized to Ensure® but who stopped consuming it at some point in time

2 Significant difference in the proportion of patients entering hospital in no Ensure® vs Ensure®-stopped ($p<0.01$)

a,b,c Totals of days in hospital or work missed when followed by different letters are significantly different ($p<0.01$) among the Ensure® compliance groups

Figure 1:

DISTRIBUTION OF PATIENTS BY YEAR OF DIAGNOSIS OF CROHN'S DISEASE



7

Figure 2:

DISTRIBUTION OF PATIENTS BY MONTH OF DIAGNOSIS OF CROHN'S DISEASE

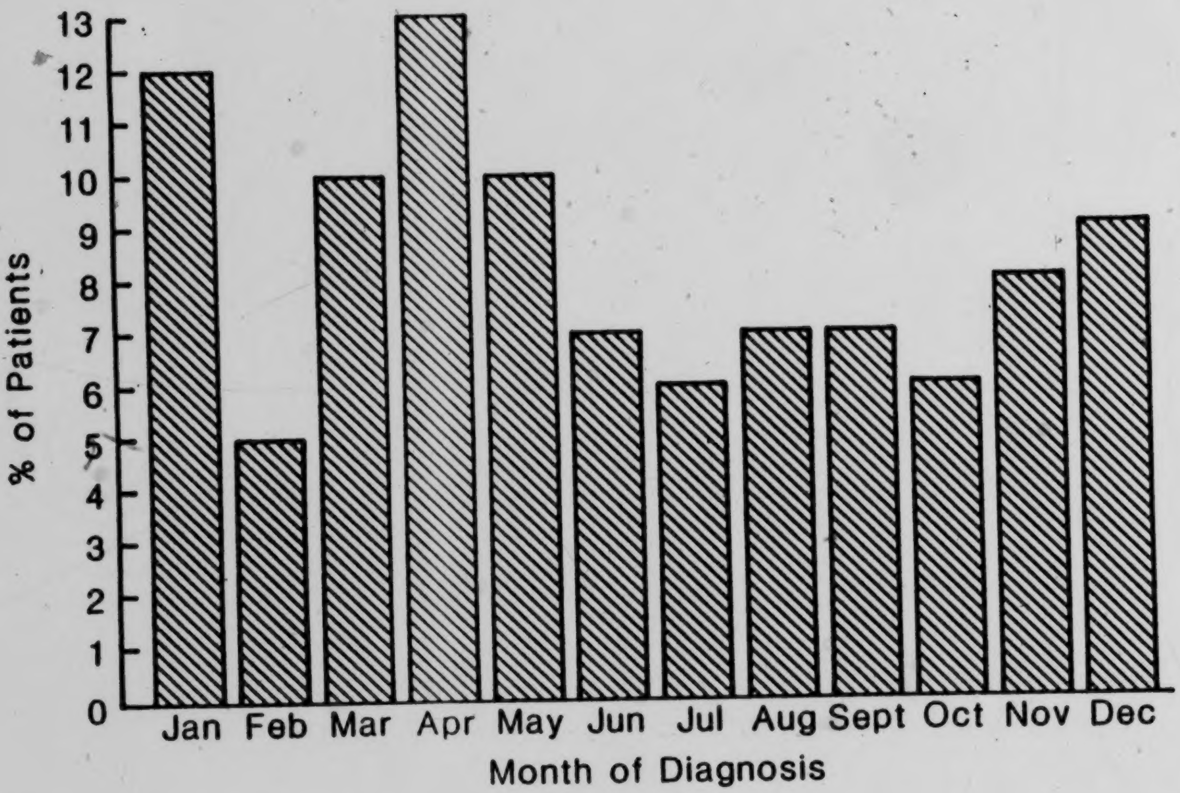


Figure 3:

DISTRIBUTION OF CROHN'S DISEASE ACTIVITY INDEX AT STUDY ENTRY

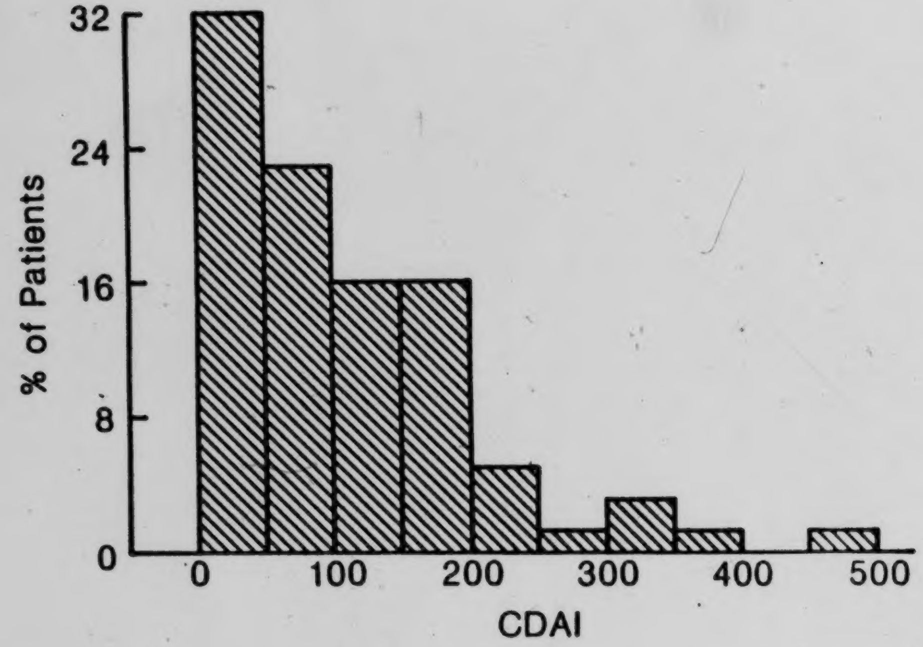


Figure 4:

SPEARMAN CORRELATION COEFFICIENTS AMONG INDICES OF CROHN'S DISEASE ACTIVITY

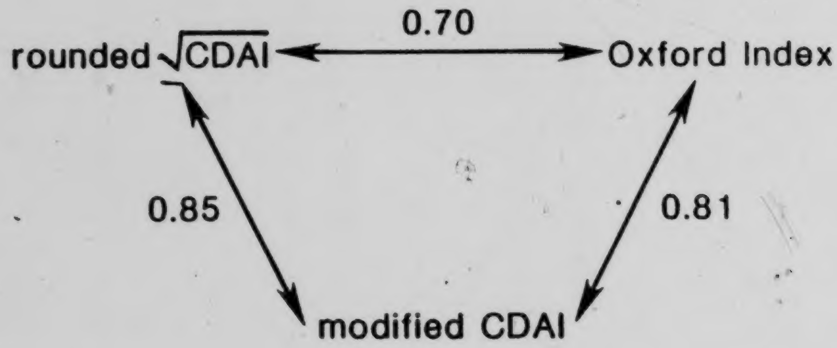

0.70
rounded √CDAI
Oxford Index
0.85
0.81
modified CDAI

Figure 5:

EFFECT OF COUNSELLING
ON THE CDAI

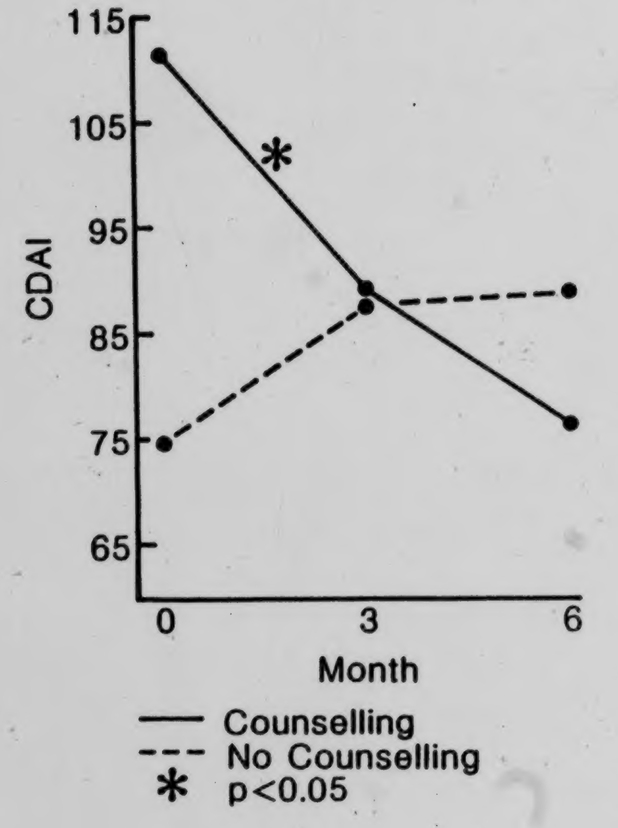


Figure 6:

CROHN'S DISEASE ACTIVITY INDEX
GREATER THAN 150

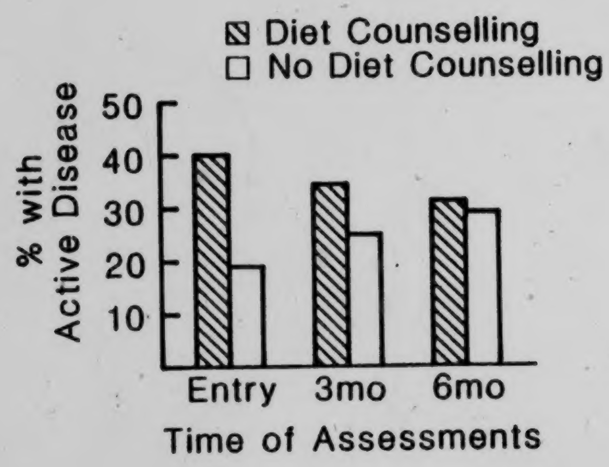
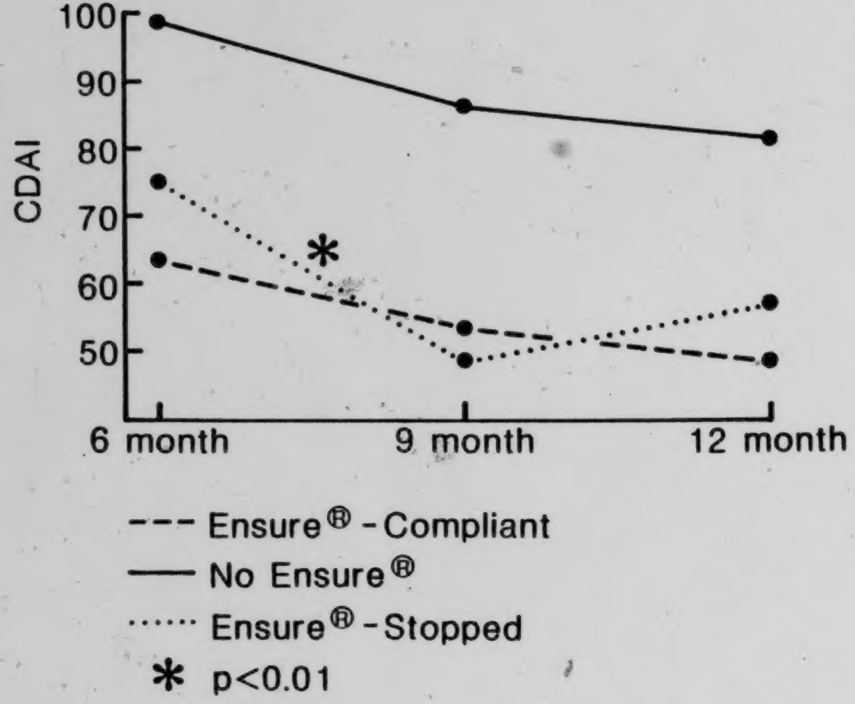


Figure 7:

EFFECT OF ENSURE® COMPLIANCE ON CDAI



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Appendix 1

Entry Questionnaire

Patient Number ______________

Study Group ______________

Date ______________

Patient Background

1. Name: ______________
2. Address: ______________
3. Phone number: home ________ work ________
4. Sex: M___ F___
5. Date of birth: ______________ Age: ________
6. Occupation: ______________
7. Years of schooling: ______________
8. Level of schooling: primary ________
    secondary ________
    technical school ________
    university or college ________
9. Marital status: never married ________
    married ________
    common law ________
    separated ________
    divorced ________
    widowed ________
10. Religion: ______________
11. Race: ______________
12. Do you smoke? no ______
    yes ______ cigarettes ________
        cigarettes/day ________
        cigars ________
        pipe ________

    Have you ever smoked regularly? no ______
    yes ______ cigarettes ________
        cigarettes/day ________
        cigars ________
        pipe ________
    if "yes", for how long did you smoke? ________
13. Does anyone else in your family have inflammatory bowel disease? (name, relationship)

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Medical History

1. Site of Crohn's Disease: small bowel ________
small bowel and colon ________
colon ________
other ________

2. Surgery related to Crohn's Disease: yes ________
no ________

3. Site of surgery: small bowel ________
colon ________
unknown ________

4. Length of bowel resected (cm): ________

5. Ileostomy/colostomy: yes ________
no ________
unknown ________

6. Renal calculi: yes ________
no ________
unknown ________

7. Metabolic bone disease: yes ________
no ________
unknown ________

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Anthropometric Measurements

1. Height ________________

2. Present weight ________________

   Usual weight _______________

   % ideal weight for height _____________

3. Mid-arm circumference ____________

   % ideal ____________

4. Skin-fold _______________

   % ideal _____________

5. Muscle circumference _____________

   % ideal _____________

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Dietary Information

1. Are you presently following a special diet? yes ________
no ________

If "yes", is it a: reducing (calorie restricted) diet ________
low residue diet ________
high fiber diet ________
bran or fiber supplement each day ________
milk (or lactose) restricted diet ________
other ________________________________

2. Are you allergic to or intolerant to any foods? yes ________
no ________

If "yes", what is the food? milk ________
fried or spicy foods ________
"gassy" vegetables (cabbage, onion) ________
raw fruits/vegetables, juices ________
other ________________________________

Are there any foods you particularly dislike?

3. Are you presently taking any vitamin or mineral supplements or injections?
yes ________
no ________

If "yes": Brand Amount/day

4. Are you presently taking any medication (Prednisone, SAS, ASA, laxatives, sedatives)? yes ________
no ________

If "yes": Brand Amount/day

5. Are you taking oral contraceptives? yes ________
no ________

If "yes", for how long? ______________

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INFLAMMATORY BOWEL DISEASE ACTIVITY INDEX

Name ______________________________

Date ______________________________

1. Number of liquid or very soft stools

2. Abdominal pain -
   - 0 = none
   - 1 = mild
   - 2 = moderate
   - 3 = severe

3. General well being -
   - 0 = generally well
   - 1 = slightly under par
   - 2 = poor
   - 3 = very poor
   - 4 = terrible

4. Complications - underline
   1. joint aches or pains, sore back
   2. red eye
   3. skin rash, sores in mouth
   4. anal fissure, fistula, abscess
   5. other fistula
   6. fever over 100°F

5. Body weight

   now ____________

   your usual weight ____________

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CROHN'S DISEASE ACTIVITY INDEX (CDAI)

Name ________________________

DATE ____________________

1. Number of liquid of very soft stools (sum x 2) ______
2. Abdominal pain (sum x 5) ______
3. General well being (sum x 7) ______
4. Complications (underline) (sum x 20) ______

   a. arthritis/arthralgia/sore back
   b. iritis/uveitis
   c. erythema nodosum/pyoderma gangrenosum/aphthous stomatitis
   d. anal fissure, fistula, abscess
   e. other fistula
   f. fever over 100°F

5. Taking Lomotil/opiates for diarrhea (x 30)

   Imodium
   Codeine

   0 = no
   1 = yes

6. Abdominal mass (x 10)

   0 = none
   2 = questionable
   5 = definite

7. Hematocrit (± x 6)

   M 47 - C, F 42 - C

8. Body weight (P/S x 100%, ± x 1)

   presently lb/kg ______
   standard lb/kg ______

TOTAL (CDAI)

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Nutrient Intakes

Nutrient	Day 1	Day 2	Average	Intake plus supplement	RDA
Energy (kcal)					
Protein (g)					
Fat (g)					
Carbohydrate (g)					
Crude fiber (g)					
Dietary fiber (g)					
Calcium (mg)					800
Phosphorus (mg)					800
Iron (mg)					M-10, F-18
Vitamin A (I.U.)					
Thiamin (mg)					
Riboflavin (mg)					
Niacin (mg)					
Vitamin C (mg)					60
Pantothenic acid (mg)					4-7
Vitamin B_6 (mg)					M-2.2, F-2.0
Vitamin B_{12} (ug)					3
Carotene (I.U.)					2000
Preformed vitamin A (I.U.)					2000
Retinol equivalents					M-1000, F-800
Free folate (ug)					200
Total folate (ug)					400
Sugars (g)					
Starches (g)					
Cholesterol (mg)					

Distribution of total calories	Ideal distribution
% from protein ____________	10-20%
% from fat ____________	30-40%
% from carbohydrate ____________	40-60%

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Lab Data

Hematology		Standard
Hemoglobin (g/dl)	______	M 13-17, F 11-16
Hematocrit (%)	______	M 38-50, F 34-46
Serum iron (ug/dL)	______	M 65-145, F 50-130
Serum ferritin (ug/L)	______	M 25-465, F 15-200
Transferrin saturation (%)	______	20-45
TIBC (ug/dL)	______	250-400
WBC ($x10^9$/L)	______	4.0-9.0
Total lymphocytes ($x10^9$/L)	______	1.5-3.5
RBC ($x10^{12}$/L)	______	M 4.3-5.7, F 3.8-5.2
MCV (fL)	______	83-97

Biochemistry		
Serum albumin (g/dL)	______	3.0-4.8
Serum protein (g/dL)	______	5.8-8.0
Serum calcium (mg/dL)	______	8.0-10.2
Serum magnesium (mg/dL)	______	1.7-2.6
Serum phosphorus (mg/dL)	______	2.5-4.8
Creatinine height index (%)	______	90

Urine		
Urinary oxalate (mg/day)	______	10-40
Urinary phosphorus (mg/day)	______	0-1000
Urinary calcium (mg/day)	______	50-200

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Malabsorption Screen		Standard
Serum vitamin A (ug/L)		300-900
Serum carotene (ug/dL)		50-250
Alkaline phosphatase (IU/L)		40-110
Serum zinc (ug/dL)		60-150
Serum copper (ug/dL)		70-140
Serum folate (ug/L)		1.7-8.6
Rbc folate (ug/L)		245-971
Serum vitamin B_{12} (ng/L)		140-520
Serum vitamin C (umol/L)		30-85
Wbc vitamin C (umol/L)		0.7-1.7
Prothrombin time (sec.)		10.0-12.8

Feces		
Fecal fat (g/day)		0-5
Fecal bile acids (g/day)		0.1-0.4
Fecal weight (g/day)		250

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Summary of Counselling Session

Nutritional Assessment Summary

1. Nutrient intake - food groups:

individual nutrients:

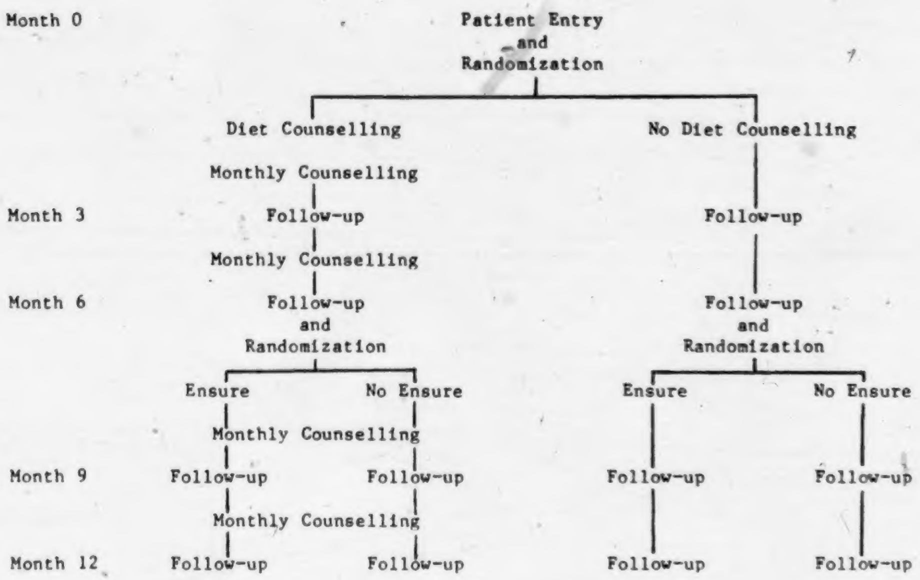
2. Anthropometric measurements, weight change -

3. Lab data, C.D.A.I. -

4. Summary of dietary counselling goals -

Appendix 2

Course of Study


Month 0
Patient Entry and Randomization
Diet Counselling
No Diet Counselling
Monthly Counselling
Month 3
Follow-up
Follow-up
Monthly Counselling
Month 6
Follow-up and Randomization
Follow-up and Randomization
Ensure
No Ensure
Ensure
No Ensure
Monthly Counselling
Month 9
Follow-up
Follow-up
Follow-up
Follow-up
Monthly Counselling
Month 12
Follow-up
Follow-up
Follow-up
Follow-up

Appendix 3
Follow-up Information

Name____________________

Date____________________

Session Number____________________

1. Is there any change in the types or amounts of vitamin and mineral supplements, injections or medications, or smoking habits since last session? yes_____ no_____

   If "yes", describe:

2. Is there any change in tolerance to specific foods or in general likes and dislikes since last session? yes_____ no_____

   If "yes", describe:

3. How many cans of Ensure have you consumed since last session?__________

   % of prescribed cans__________

   Mean cans of Ensure consumed per day__________(0.0)

Problems consuming Ensure:	diarrhea	yes_____	no_____
	gas	yes_____	no_____
	abdominal pain, cramps	yes_____	no_____
	bloating	yes_____	no_____
	coats tongue and teeth	yes_____	no_____
	dislike flavor	yes_____	no_____
	decreases food intake	yes_____	no_____
	other(describe)	yes_____	no_____
	stopped taking Ensure	yes_____	no_____

5. Have you had Crohn's related surgery since last session? yes_____ no_____

   (includes laparotomy, perianal, gall stones, kidney stones and resection)

Appendix 3 continued

6. How many days have you spent in hospital due to Crohn's disease since last session? ______

7. How many days have you been unable to go to work due to Crohn's disease since last session? ______

8. Have you been sick for any other reason since last session? yes_____
no_____

If "yes", what was the reason?

Appendix 4
Composition of Ensure®

INGREDIENTS: Water, corn syrup solids, sucrose, sodium and calcium caseinates, corn oil, soy protein isolate, potassium citrate, magnesium chloride, soy lecithin, calcium carbonate, potassium chloride, sodium hexametaphosphate, choline chloride, ascorbic acid, carrageenan, zinc sulfate, ferrous sulfate, sulpha-tocopheryl acetate, niacinamide, manganous chloride, calcium pantothenate, cupric sulfate, thiamine hydrochloride, vitamin A palmitate, pyridoxine hydrochloride, riboflavin, phylloquinine, vitamin D_2, biotin, folic acid, cyanocobalamin and artificial flavoring.

APPROXIMATE ANALYSIS:	per 100 ml	per can (235 ml)
Protein(g)	3.72	8.74
Fat (g)	3.72	8.74
Linoleic acid (as triglycerides)(g)	2.00	4.70
Carbohydrate (g)	14.50	34.08
Choline (g)	0.06	0.14
Ash (g)	0.59	1.39
Moisture (g)	84.40	198.34
Kilcalories	106	250

DISTRIBUTION OF CALORIES: protein 14%, fat 31%, carbohydrates 54.5%

OSMOLALITY: 460 mOsm/L

VITAMINS AND MINERALS:	per 100 ml	per can (235 ml)
Vitamin A (IU)	264.00	620.40
Vitamin D (IU)	21.00	49.35
Vitamin E (IU)	3.17	7.45
Vitamin K_1 (µg)	14.77	34.71
Vitamin C (mg)	15.86	37.27
Folic acid (mg)	0.02	0.05
Vitamin B_1 (mg)	0.16	0.38
Vitamin B_2 (mg)	0.18	0.42
Vitamin B_6 (mg)	0.21	0.49
Vitamin B_{12} (µg)	0.63	1.48
Niacin (mg)	2.10	4.94
Biotin (mg)	0.02	0.04
Pantothenic acid (mg)	0.53	1.25
Sodium (g)	0.07	0.17
Potassium (g)	0.12	0.28
Chloride (g)	0.11	0.26
Calcium (g)	0.05	0.12
Phosphorus (g)	0.05	0.12
Magnesium (g)	0.02	0.05
Iodine (µg)	8.50	19.98
Manganese (mg)	0.21	0.49
Copper (mg)	0.11	0.26
Zinc (mg)	1.60	3.76
Iron (mg)	0.95	2.23

Appendix 5

Harvey and Bradshaw Modified Crohn's Disease Activity Index, and Oxford Index

Modified CDAI:	1. Bowel motions	0-5
	2. Abdominal pain	0-3
	3. General well-being	0-4
	4. Complications	1 each
	5. Abdominal mass	0-3

Conversion of CDAI to modified CDAI:

1. Bowel motions: if previous day's total was 0, code 0
" 1-3, code 1
" 4-6, code 2
" 7-9, code 3
" 10-12, code 4
" above 12, code 5

2. Abdominal pain: if previous days' pain was none, code 0
" mild, code 1
" moderate, code 2
" severe, code 3

3. General well-being: if previous day was generally well, code 0
" slightly under par, code 1
" poor, code 2
" very poor, code 3
" terrible, code 4

4. Complications: presence of any complications listed in question 4 of CDAI, code 1 each to a maximum of 6.

5. Abdominal mass: no mass, code 0
questionable mass, code 1
definite mass, code 3

Appendix 5 continued

Oxford Index: score 1 for each of
1. Bowel motions above 6 per day
2. Abdominal pain present
3. Other complications: joints, eyes, skin
    fistula
    perianal complications
    temperature over 38°C
    abdominal mass present
    hemoglobin below 10 g/dL
    wasting

Conversion of CDAI to Oxford:
1. Bowel motions: if previous day's total was above 6, code 1
2. Abdominal pain: if previous day's pain was mild to severe, code 1
3. Other complications: joints/eyes/skin, code 1
    intestinal fistula, code 1
    perianal complications (including fissure, fistula, abscess), code 1
    fever over 100°F, code 1
    abdominal mass questionable or definite, code 1
    hemoglobin below 10 g/dL, code 1
    body weight below 90% ideal, code 1

Appendix 6
Reference Ranges and Methodology

TEST	UNITS	REFERENCE RANGE	COEFFICIENT OF VARIATION	REFERENCE
Hb	g/dL	M 13-17 F 11-16	0.9	Ortho ELTT800 Operators Manual Coulter S Plus IV Operators Manual
HCT	%	M 38-50 F 34-46	1.1	"
Rbc	$X10^{12}/L$	M 4.3-5.7 F 3.8-5.2	0.8	"
MCV	fL	83-97	0.5	"
WBC	$x10^{9}/L$	4.0 - 9.0	1.4	"
Tot. lymph.	$x10^{9}/L$	1.5 - 3.5	-	"
Prothrombin	sec	10. 0 - 12.8	1.8	General Diagnostics Coagamate Operators Manual
Fe	µg/dL	M 65-145 F 50-130	4.0	DuPont ACA Iron Methodology
TIBC	µg/dL	250 - 400	4.5	DuPont ACA, Iron Methodology
Transferrin Saturation	%	20 - 45	-	Calculation = Fe/TIBC
Ferritin	µg/L	M 25-465 F 15-200	15.4	Luxton AW, Walker WHC, Gauldie J, Ali, MAM, Pelletier, C., Clin. 23 683 (1977)
Vitamin B_{12}	ng/L	140 - 520	13.5	Lau K-S, Gottlieb, C., Wasserman et al. Blood 26 202 (1965)
Folate	µg/L	1.7 - 8.6	12.5	Longo, DL, Herbert, V., J. Lab. Clin. Med. 87 138 (1976)
Rbc folate	µg/L	245 - 971	11.7	Mortensen, E. Clin. Chem. 22 982 (1976)
Tot. prot.	g/dL	5.8 - 8.0	1.1	Tech. SMA 12 Method SF4, 0014FJS
Alb	g/dL	3.0 - 4.8	1.7	Tech. SMA 12 Method SF4, 0030FE5 (1975)
Urea N	mg/dL	7 - 22	1.8	Tech. SMA 12 Method SF4, 0001FF5, (1975)

Appendix 6 continued

TEST	UNITS	REFERENCE RANGE	COEFFICIENT OF VARIATION	REFERENCE
Creatinine	mg/dL	0.6 - 1.4	2.0	Tech. SMA 12 Method SF4 0011FF54 (1975)
Calcium	mg/dL	8.0 - 10.2	1.5	Tech. SMA 12 Method SF4, 0003FE5 (1975)
Magnesium	mg/dL	1.7 - 2.6	3.4	Perkin Elmer Atomic Absorption Manual
Copper	µg/dL	70 - 140	5.5	Parker, M, Humoller, F., Mahler, D. Clin. Chem. 13 40 (1967)
Zinc	µg/dL	60 - 150	5.9	Meret, S, Henkin, R.I. Clin. Chem. 17, 369 (1971)
Phosphorus	mg/dL	2.5 - 4.8	1.3	Tech SMA 12 SF4, 0004FF5 (1975)
Alk. phos.	IU/L	40 - 110	7.8	Tech. SMA 12 Method SFE 0006 FGS (1975)
Carotene	µg/dL	50 - 250	5.8	Wenger, J. Am. J. Med. 22, 373 (1957)
Vitamin A	µg/L	300 - 900	6.2	Smith, F.R., Goodman, D.S., New Eng. J. Med. 294 805 (1976)
Vitamin C	µmol/L	30 - 85	6.0	Denson, K.W. & Bowers, E.F. Clin. Science 21 157 (1961)
WBC Vitamin C	µmol/L	0.7 - 1.7	15.0	Denson, K.W. & Bowers, E.F. Clin. Science 21, 157 (1961)
Urine				
Urea N	g/day	6 - 12	2.6	Beckman Astra Urea Manual (1979)
Creatinine	g/day	M 1.0 - 1.7	3.3	Beckman Astra Creatinine Manual (1979)
Calcium	mg/day	50 - 200	1.6	Perkin Elmer Atomic Absorption Manual
Phosphate	mg/day	0 - 1000	1.4	DuPont ACA Phosphorus Methodology
Oxalate	mg/day	10 - 40	15.0	Koch, G.H., Strong, F.M. Anal. Biochem. 27, 162 (1969)
Feces				
Fat	g/day	0 - 5	7.4	Van de Kamer, J., Huiniuk, H.B., Wyers, H.A. J. Biol. Chem. 177, (1969)
Bile acids	g/day	0.1 - 0.4	10.0	Chettaway, M.J., Losawsky, M.S. Clin. Chem. Acta. 64 127 (1975)

Appendix 7

Nutrient Intake of Out-Patients with Crohn's Disease*

Nutrient	Males (n=23) Mean ± SD	Females (n=24) Mean ± SD
Energy (kcal)	2861 ± 912	1867 ± 866
Protein (g)	103 ± 37	68 ± 31
Fat (g)	116 ± 44	74 ± 39
Carbohydrate (g)	333 ± 116	232 ± 114
Crude Fiber (g)	4.3 ± 1.6	3.3 ± 2.2
Dietary Fiber (g)	-	13.3 ± 9.3
Calcium (mg)	1048 ± 675	707 ± 526
Phosphorus (mg)	1679 ± 666	1114 ± 562
Iron (mg)	17.6 ± 7.1	11.7 ± 6.2
Vitamin A (IU)	6353 ± 4641	5131 ± 4422
Carotene (IU)	3828	3973
Preformed Vitamin A (IU)	2597	2194
Thiamin (mg)	1.9 ± 1.9	1.4 ± 1.9
Riboflavin (mg)	2.4 ± 1.1	1.7 ± 1.1
Niacin (mg)	-	-
Vitamin C (mg)	187 ± 181	135 ± 120
Vitamin B_{12} (µg)	4.7 ± 3.8	5.3 ± 7.1
Free Folate (µg)	-	-
Total Folate (µg)	211 ± 90	185 ± 122
Sugar (g)	-	121 ± 76
Cholesterol (mg)	-	-

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* Hodges, P. Nutritional assessment of out-patients with Crohn's Disease. M.Sc. Thesis. Faculty of Home Economics, University of Alberta, 1981.

CURRICULUM VITAE

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PERSONAL

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ACADEMIC

1974 - B.A. in French, University of Saskatchewan, Saskatoon
1979 - B.Sc. in Nutrition, University of Alberta, Edmonton
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WORK EXPERIENCE

May 1973 to September 1973 - Assistant researcher, Department of Agriculture, University of Saskatchewan, Saskatoon

May 1974 to June 1976 - Researcher, Film D.R. Productions, Edmonton

May 1979 to August 1980 - Nutritionist, Milk Foundation of Edmonton, Edmonton

AWARDS

1970 - Saskatchewan Matriculation Scholarship
1971, 1972, 1973 - University of Saskatchewan Undergraduate Scholarship
1971 - Student exchange program, France
1972 - French immersion course bursary
1977, 1978 - University of Alberta Undergraduate Scholarship
1978 - The David Butchart Pope Scholarship
The Barbara McLaren Prize in Nutrition
The Gretta Shaw Simpson Memorial Prize
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1982, 1983 - Studentship grant, Alberta Heritage Foundation for Medical Research

PUBLICATIONS

1. "Nutrition and Crohn's Disease". In the Canadian Foundation for Ileitis and Colitis Journal. Vol. 2, No. 1. Summer 1981.
2. "Health Foods and Food Fads". (educational booklet) (soon to be printed by the Milk Foundation of Edmonton)

ABSTRACTS

The Effect of Diet Counselling on Crohn's Disease. Presented at the annual meeting of the Royal College of Physicians & Surgeons, Montreal, September 1984.